Queen Margaret University

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DEVELOPMENT OF A PROGNOSTIC MODEL FOR FISTULA MATURATION IN PATIENTS WITH ADVANCED RENAL FAILURE

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List of Abbreviations

ABPI	Ankle Bracheal Pressure Index
ACL-TOP	Trademark of Instrumentation Laboratory, UK
ADA	American Diabetic Association
AV	Arteriovenous
AVF	Arteriovenous Fistula
AVG	Arteriovenous Grafts
BB	Brachiobasilic
BC	Brachiocephalic
BMI	Body Mass Index
BP	Blood Pressure
Ca	Serum Calcium
CI	Confidence Interval
CKD	Chronic Kidney Disease
cNOS	Contitutive Nitric Oxide Synthase
CVC	Central Venous Catheter
DBP	Diastolic Blood Pressure
DM	Diabetes Mellitus
DOPPS	Dialysis Outcome and Practice Pattern Study
DOQI	Dialysis Outcomes Quality Initiatives
EC	Endothelial Cell
eGFR	Estimated Glomerular Filtration Rate
EQC	External Quality Control
ERF	Established Renal Failure
ESRD	End Stage Renal Disease
FTM	Failure to Mature

HbA1C	Glycosylated Haemoglobin
HCO_3	Bicarbonate
HD	Haemodialysis
HDL	High Density Lipoprotein
HEMO Study	Haemodialysis Study
HTN	Hypertension
IDMS	Isotope Dilution Mass Spectrometry
iNOS	Inducible Nitric Oxide Synthase
INR	International Normalization Ratio
IQC	Internal Quality Control
ISE	Ion Selective Electrode
ISI	International Sensitivity Index
K	Serum Potassium
KoA	Mass Transfer-area Coefficient
MDRD	Modification of Diet in Renal Disease
MHz	Mega Hertz
Na	Serum Sodium
NF-kB	Nuclear Factor - kappaB
NHS	National Health Service
NHANES	National Health and Nutrition Examination Survey
NIBSC	National Institute for Biological Standards and Controls
NICE	National Institute for Health and Clinical Excellence
NKF	National Kidney Foundation
NO	Nitric Oxide
NOS	Nitric Oxide Synthase
NPV	Negative Predicted Value

OR	Odds Ratio
P	Significance level
PD	Peritoneal Dialysis
PPV	Positive Predicted Value
PT	Prothrombin Time
PTFE	Polytetrafluoroethylene
PVD	Peripheral Vascular Disease
RC	Radiocephalic
ROC	Receiver Operating Curve
RRT	Renal Replacement Therapy
SBP	Systolic Blood Pressure
SPSS	Statistical Package for the Social Sciences
TC	Total Cholesterol
TG	Triglyceride
TGF β 1	Transforming Growth Factor beta 1
TNF- α	Tumor Necrosis Facor Alpha
UK	United Kingdom
UK NEQAS	United Kingdom National External Quality Assessment Service
UKRR	UK Renal Registry
US	United States
USRDS	United States Renal Data System
VA	Vascular Access
VSMC	Vascular Smooth Muscle Cell
WHO	World Health Organisation

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Abstract

Introduction

A suitable type of vascular access has to be created to establish a connection between the circulation system of the patient and the haemodialysis cycle. The arteriovenous fistula (AVF) is considered to provide the best long-term functional vascular access, with reduced risk of thrombosis or infection and cost-effective. However, significant numbers of AVF, which fail to develop sufficiently for dialysis, are 28-53% of cases. This study aimed to explore the potential influence of blood markers and factors on the maturation of AVF, in patients who have undergone vascular access surgery and to develop and validate a prognostic model to determine the success of AVF maturation.

Methods

Data from 300 patients was retrieved who had undergone AVF surgery between the years 2006 and 2009, from the Royal Infirmary of Edinburgh. A prognostic model was developed for the prediction of maturation of AVF using backward stepwise logistical regression. This data was analysed using univariable, multivariable logistic regression. Model performance was assessed, using the receiver operating characteristics (ROC) curve and Hosmer and Lemeshow goodness of fit test. A prognostic model was validated with the prospective data of 100 patients who had undergone AVF surgery between the years 2009 and 2011, from the Royal Infirmary of Edinburgh.

Results

Three variables were identified, which independently influenced fistula maturation. Males were twice as likely to undergo fistula maturation, compared to that of females (odds ratio (OR) 0.514; 95% confidence interval (CI) 0.308 to 0.857). Patients with no evidence of Peripheral Vascular Disease (PVD) were three times more likely to mature their fistula (OR 3.140; 95% CI 1.596 to 6.177). A pre-operative vein diameter greater than 2.5mm resulted in a fivefold increase in fistula maturation compared to a vein size less than 2.5mm (OR 4.532; 95% CI 2.063 to 9.958). The model for fistula maturation had good discrimination as indicated by area under the ROC curve 0.677 and calibration as indicated by Hosmer and Lemeshow test (p = 0.79). The model discriminatory power was confirmed in the prospective study (validation data set) with area under the receiver operating curve was 0.59 and calibration indicated by Hosmer and Lemeshow test ($p > 0.05$).

Conclusion

Successful vascular access provision is the foundation on which successful haemodialysis is built. This study has found that female gender, history of PVD and vein diameter less than 2.5 mm are the negative significant independent clinical predictors of maturation of arteriovenous fistula.

CHAPTER 1

INTRODUCTION

1.1 Kidney Failure and Dialysis

Chronic Kidney Disease (CKD) is a critical condition with considerable public health implications. It affects a significant proportion of the general population and when progressive, has an increasing influence on morbidity and mortality. An estimated 10% of adults (more than 20 million people) in the United States have CKD (Centres for Disease Control and Prevention 2014). In England in 2008/09 there were 1,739,443 people aged 18 and over who were registered with stage 3 to 5 CKD (NHS Kidney Care 2010). According to the United States Renal Data System (USRDS 2011), more than 87,000 people die from causes related to kidney failure each year. The two most important corollaries of CKD are cardiovascular disease and End Stage Renal Disease (ESRD). Once a patient reaches established kidney failure, his/her quality of life becomes poor and the life expectancy is considerably shortened. Through the provision of Renal Replacement Therapy (RRT) survival and quality of life of ESRD patients can be markedly improved. Another important determinant of ESRD on a global scale is diabetic nephropathy, which has had a growing prevalence since the beginning of the 21st century. The cause of this phenomenon is the increasing proportion of individuals who develop type 2 diabetes mellitus (USRDS 2011).

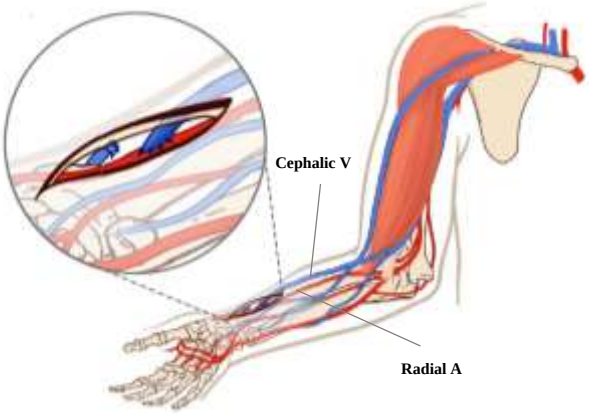
Haemodialysis and peritoneal dialysis are two corresponding treatments in ESRD. Despite the right that patients have to choose between these two treatments, often this is over ruled by factors, which are more essential, such as access to haemodialysis centre, difficulty in the creation or maintenance of vascular access, or

the urgent necessity to treat people in a critical condition (uraemic emergencies). In order to ensure that the suitable treatment is selected, CKD patients have to be referred to a kidney specialist as early as possible.

1.2 Vascular Access and Arteriovenous Fistula

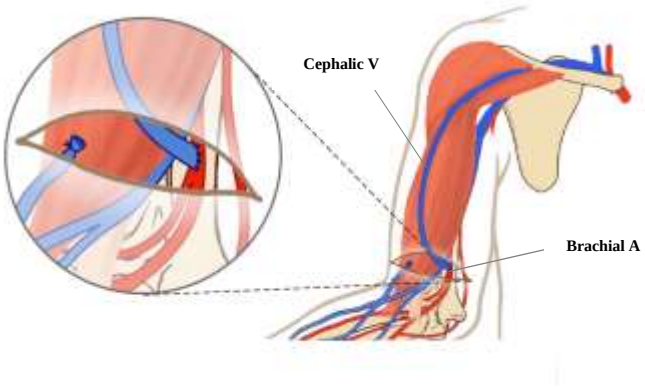
The efficiency of haemodialysis treatment relies on a functional status of vascular access (VA). According to the National Institute for Health and Clinical Excellence Guidelines (NICE) (2008), VA and its related problems represent the main factors that determine a rise in the rate of incidence of the disease among haemodialysis patients and, consequently, a rise in the healthcare expenses. Vascular access can be divided into three categories: arteriovenous fistula (AVF), central venous catheter (CVC) and arteriovenous graft (AVG). As highlighted by several researchers (Banerjee 2009; Agarwal *et al*. 2007; Combe *et al.* 2001; Hoen *et al.* 1995), CVC has a number of disadvantages, including a considerable risk of infection and mortality. It also has negative implications for the use of a fistula for dialysis. In contrast, AVF is the most beneficial method, as it has a low risk of infection and mortality, and can ensure long-term functional access (Iyem 2011; Dixon *et al*. 2002; Feldman *et al.* 1996). Furthermore, there are three configurations of native AVF that can be used for haemodialysis providing flexibility of approach depending on risk factors of the individual patient. Figure 1 shows the three configurations of native arteriovenous fistula used for haemodialysis, that are radiocephalic, brachiocephalic, and brachiobasilic fistula (Fitzgerald *et al.* 2004).

Figure 1. Radiocephalic, Brachiocephalic and Brachiobasilic AVF (Adopted from Vachharajani 2010)



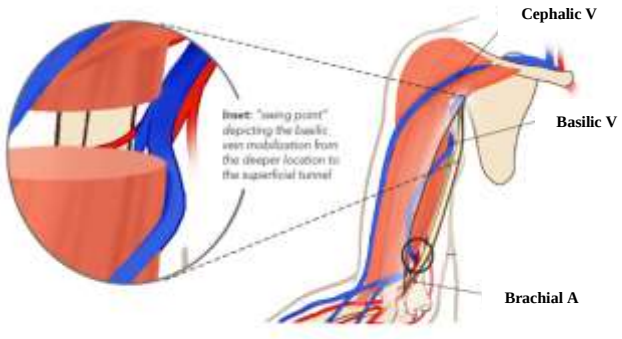
The radiocephalic arteriovenous fistula at the wrist utilizes the forearm segment of the cephalic vein and radial artery.

Radiocephalic AVF



The brachiocephalic fistula at the elbow utilizes the upper arm segment of the cephalic vein and brachial artery.

Brachiocephalic AVF



The basilic vein is mobilized from its usual location and transposed superficially through the deep fascia in the upper arm to create the brachiobasilic AVF.

Brachiobasilic AVF

Both European and North American medical guidelines highly recommend the use of AVF (National Kidney Foundation – Kidney Disease Outcome Quality Initiative [NKF-KDOQIa] 2006; Tordoir *et al.* 2007). As explained by Stehman-Breen *et al.* 2000), the decision to use AVF is based on a number of patient characteristics, including age, sex, education, disability or co-morbidities including obesity, PVD, ischaemic heart disease, and diabetes mellitus. The likelihood of European population undergoing haemodialysis to have AVF in Dialysis Outcomes and Practice Patterns Study one (DOPPS-1) was found to be considerably high (Pisoni *et al.* 2002).

AVFs are the preferred vascular access type for haemodialysis (National Kidney Foundation 2001). However, maintaining an autologous fistula has become more important over the last three decades due to diabetes, vascular disease and an ageing population (Chiulli *et al.* 2011). Compared with CVCs or AVGs, AVFs present fewer interventions, longer patency rates, low infections and overall lesser mortality rates. An autologous fistula is found to have a longer patency rate and, as such, its use on dialysis patients has been intensely advocated (Tonnessen and Money 2005). The cost of vascular access related care was found to be more than five-fold higher in patients with AVG compared to patients with a functioning AVF (Lee *et al.* 2002). The Choices for Healthy Outcomes in Caring for ESRD (CHOICE) Study examined mortality based on access type in 616 haemodialysis patients for up to 3 years of follow-up. CVCs and AVGs were associated with approximately 50% and 26% increased mortality respectively, compared with AVFs (Astor *et al.* 2005). Furthermore, guidelines have encouraged the use of the patient's own blood vessels for the construction of VA as AVG and CVC are made from prosthetic graft

material, which has a low patency rate and a high mortality rate (Pisoni *et al.* 2009; Tordoir *et al.* 2007). There are two conditions that a fistula must fulfil in order to be efficient for dialysis: a sufficiently large diameter for the process of cannulation and sufficient blood flow so that the dialysis circuit functions properly. As noted by Lomonte *et al.* (2005), expansion in diameter and increase in blood flow within the draining venous vessel happen immediately subsequent to the construction of the fistula and is maximal within a few weeks. Traditionally a period of six weeks has been allowed for maturation; however, some dialysis units have advocated the use of fistula within two weeks (Saran *et al.* 2004). VA complications represent the main factor that determines a rise in the morbidity among haemodialysis patients and, consequently, a rise in the healthcare expenses. According to the NICE Guidelines (2008), the National Health Service in the United Kingdom consumes 2% of its financial resources to renal replacement therapy.

1.3 Success of Arteriovenous Fistula

The blood flow rate, which a functional AVF is capable to uphold for the whole length of the dialysis treatment, with no recirculation is 350-400 ml/min. The complications most often associated with arteriovenous fistula are thrombosis, stenosis, aneurysm, ischaemia, and steal syndrome (Allon and Robbin 2002). As noted by Beathard *et al.* (2003), vessel obstruction during the initial three months following construction can lead to early fistula failure, which is an important factor affecting fistula prevalence. The rate of use of AVF on haemodialysis patients is also noted to be affected by the insufficient development of fistulae. As such, it is important to identify and intervene early in fistulae which are likely to fail. As noted

by Beathard *et al.* (2003), most fistulae that experience early failure exhibit access stenosis. This is a process, which unfolds gradually, ultimately resulting in complete occlusion, which causes access thrombosis (Asif *et al*. 2006).

The HEMO (Haemodialysis) trial analysed the haemodialysis access types and their associated epidemiology; in addition, the project discussed preponderance of grafts, as well as the factors that negatively affected the construction of native fistulae for haemodialysis. Obesity was indicated as one such factor (Polkinghorne *et al.* 2003; Allon *et al.* 2000). According to the Dialysis Outcomes and Practice Patterns Study (DOPPS), the success rate of AVF construction was higher in younger, male patients with a normal BMI, who did not suffer from diabetes or peripheral vascular disease. However, Weyde *et al.* (2008) revealed that there was an 85% success rate in the construction of AVFs in obese patients, demonstrating that in the pre-dialysis examination the thick adipose tissues offered protection to the vessels in the lower arm from iatrogenic damage. The patency rate of AV grafts is approximately 49% at one year and 30% at two years (Pisoni *et al.* 2002) and in the case of dialysis patients relying on AV grafts, they have to be subjected to one or more operations annually in order to treat thrombosis and ensure proper functioning of the graft (Glanz 1991).

1.4 Rationale and Aims of the Study

1.4.1 Rationale of the Study

Recently, elderly patients and diabetics have been able to undergo dialysis therapy, due to the expansion of the selection criteria. Consequently, an increase in co-morbidity, such as atherosclerotic vascular disease, has been observed in patients

undergoing dialysis. A great number of such patients have poor vessels, which cannot support the creation of native AVF. What is more, the growing focus on patient suitability for dialysis therapy has determined that a higher blood flow rate is important as it can enhance the filtering of urea, which means that a larger number of patients can undergo dialysis without a considerable increase in the length of the treatment.

To ensure that the dialysis therapy can be efficiently undertaken, all patients need a fully developed fistula that is appropriate for the process of cannulation. In order to achieve this, several stages have to be covered, namely, pre ESRD treatment by a kidney specialist and early referral to vascular surgeons for the construction, development, and cannulation of a fistula by dialysis specialists staff. Asif *et al.* (2005) indicated that the percentage of AVFs that fail to develop sufficiently for dialysis is 28-53%. The dialysis therapy is often postponed for up to half a year or more to allow extra time for the fistula to develop; if this does not happen, the AVF is considered a failure. Corpataux *et al.* (2002) stated that the development process of AVF is complicated and it is almost impossible to settle on the precise length of time it requires to complete. Research studies conducted on predictive markers of an adequate and operative fistula have failed to reach a consensus, due to the fact that they have focused on different aspects and have used different definitions of maturation, study design, clinical factors and patient sample. Thus, surgeons are confronted with the challenge of classifying the different risk factors as well as deciding on the parameters to use in order to evaluate the possibility of successful fistula development. Multiple studies (Zadeh *et al*. 2012; Jennings *et al*. 2011; Kheda *et al*. 2010; Dember *et al*. 2008; Trimarche *et al*. 2006; Rooijens *et al*. 2005; Obialo

et al. 2003; Feldman *et al*. 2003; Mendes *et al*. 2002; Huber *et al*. 2002; Robbin *et al*. 2002) have been conducted to determine the factors associated with AVF maturation, including patient demographics (age, gender, diabetes, PVD, hypertension, smoking, obesity), AVF characteristics (type and side of arm), blood markers (lipid profile, coagulation status, uraemic status) and vein diameter. A number of studies have observed association of increasing age with early fistula failure (Lok *et al.* 2005; Golledge *et al*. 1999; Lazarides *et al*. 1996). Results of previous studies have suggested that rate of AVF maturation is higher in male than in female gender (Ernandez *et al*. 2005; Miller *et al*. 2003) and patients those already commenced dialysis before AVF creation (Zeebregts *et al*. 2002). History of diabetes (Zeebregts *et al* 2005; Ernandez *et al*. 2005) and PVD (Chan *et al*. 2008) have found to be associated with failure of AVF maturation. Multiple studies had found that hypertension (Kaygin *et al*. 2012; Palmes *et al*. 2011) and smoking (Ozdemir *et al.* 2005; Wetzig *et al*. 1985) are associated with failure of AVF maturation. Chan *et al*. (2008) observed a relation between insufficient fistula development and a high BMI (>30 kg/m^2). An observational study carried out in Finland concluded that coagulation abnormalities such as short thrombin time and high fibrinogen associated with AVF maturation failure (Salmela *et al*. 2013). Hyperlipidaemia (Gagliardi *et al*. 2011) and hyperuricaemia (Bhan *et al*. 2007) poorly predict AVF maturation. Researchers have recommended a number of pre-surgical principles relying on non-invasive (physical examination includes assessment of the distal arterial pulse and course of the superficial upper and forearm veins; duplex ultrasound imaging) and invasive (venographic assessment of veins) imaging procedures; however, factors

such as cost, time and complexity, hinder the widespread application of these principles.

As noted by Tonnessen and Money (2005), a collaborative medical effort has been made to enable more patients to undergo dialysis with a fistula. One of the essential factors that determine the success rate of fistula development is the diameter of the blood vessels. According to Malovrh (1998), if the pre-surgery vessel diameter was smaller than 1.5mm, only a 36% success rate was recorded three months after the construction of fistulae for dialysis; this percentage increased to 83% when the vessel diameter was greater than 1.5 mm. In addition, the rate of blood flow in the fistula was greater in the latter case, in contrast to the former one. Wong *et al.* (1996) corroborated these results, demonstrating that in cases where the diameter of the vein or artery was smaller than 1.5 mm, the fistula never reached complete maturation. In contrast, it was impossible to predict the success rate of fistula development when the diameter of the vessels exceeded 1.5 mm. Allon *et al.* (2001) revealed that a direct association between the vessel diameter and the success rate of fistula development could not be established when the diameter requirements for artery and vein of 2 mm and 2.5 mm, respectively, were fulfilled. No significant differences were observed during the pre-surgical mapping between diabetes and non-diabetics with regard to the diameter of the blood vessels. Nonetheless, Sedlacek *et al.* (2001) discovered that diabetics are more prone to developing vascular calcifications (64%) than non-diabetics (35%). Both the diameter of blood vessels and the rate of blood flow exhibited a rapid increase immediately after fistula creation, reaching a high point at six weeks (Lomonte *et al.* 2005).

Vascular surgeons are required to construct mature AVFs to ensure their successful maturation and proper functioning to withstand dialysis. AVFs are cheaper, last longer, have a lower infection rate, decrease morbidity, and mortality, and reduce the chances of repeat intervention (Allon 2007; Polkinghorne *et al*. 2004). The ultimate purpose is to create a functional, long-term access for dialysis, the creation of AVF being just a step towards achieving that purpose. The pre surgical assessments of the most favourable location for fistula creation as well as patient suitability are highly important, but the methods needed to carry out this assessment have not been well documented. To enhance the use of fistula it is necessary to have a comprehensive and clear understanding of the factors that affect the success rate of the procedure, and provide effective solutions. One of the main obstacles is the high incidence of early fistula failure caused by early thrombosis or insufficient development and maturation, which hinder its use for dialysis. It is noted that when considering the maturation of AVF, many areas of controversy and uncertainty persist.

1.4.2 Research Question

What are the important blood markers and patient factors that can be helpful in determining the success of fistula maturation before surgery?

1.4.3 Aims of the Study

The study aims to develop a simple, clinically practical, and user-friendly prognostic model to predict which arteriovenous fistula are likely to mature.

1.4.4 Primary Objective

The objective was to retrospectively establish the potential influence of blood markers and patients factors (risk factors, kidney function profile, coagulation profile, lipid profile, BMI, BP and vein diameter) on the maturation of arteriovenous fistula in patients who had previously undergone vascular access surgery in the Royal Infirmary of Edinburgh.

1.4.5 Secondary Objective

The objective was to prospectively explore the influence of blood markers and patient's factors on the maturation of arteriovenous fistula in patients who had recently undergone vascular access surgery in the Royal Infirmary of Edinburgh and to validate the prognostic model for the prediction of arteriovenous fistula formation.

1.5 Outline of the Thesis

1.5.1 Chapter 2 (Literature Review)

This chapter provides up-to-date evidence on aetiology, predisposing factors, clinical features and diagnosis of CKD. In addition, the current management of stage five CKD known as ESRD is explained. Furthermore, type of vascular access for haemodialysis and different configuration of AVF is provided. Finally, details of patients' factors, blood markers and maturation of AVF is discussed.

1.5.2 Chapter 3 (Methods)

This chapter provides information about the retrospective and prospective part of the study. In addition information about the research procedures such as recruitment of participants, inclusion and exclusion criteria and details of blood markers are provided. Finally, data collection and statistical method adopted is presented.

1.5.3 Chapter 4 (Results)

In this chapter, results are presented for both development and validation phases of the study. Data analysis on patient's demographics, univariate and multivariate analysis is reported. Statistical analysis to validate the developed model is also provided. Finally, external validation of the developed model is presented.

1.5.4 Chapter 5 (Discussion)

This chapter discusses the findings related to primary and secondary objectives in relation to published work and practice.

1.5.5 Chapter 6 (Conclusion)

This last chapter summarises the main findings emerging from this thesis and highlights the potential role of the developed model in the prediction of maturation of AVF before surgery. Also the strengths, limitations of the study and clinical implications is discussed.

CHAPTER 2

LITERATURE REVIEW

2. 1 Chronic Kidney Disease

2.1.1 Introduction

Kidney disease is an important condition with considerable public health implications, which are only multiplied by rising rates of diabetes mellitus, obesity, hypertension, and the ageing population (Levey *et al*. 2007). Chronic renal failure is a condition, which develops gradually and has various causes contributing to the deterioration of the kidneys, and can progress to ESRD. The definition of chronic kidney disease is based on the presence of kidney damage (albuminuria) or decreased kidney function (glomerular filtration rate < 60 mL/min per 1·73m²) for 3 months or more, irrespective of clinical diagnosis (Stevens and Levey 2009; Vassalotti *et al.* 2007; NKF-KDOQIb 2006). Yu (2003) stated that the rate of decline, termed progression, is characterised by a great deal of variation. It affects a significant proportion of the general population and, when progressive, has an increasing impact on morbidity and mortality. In the United Kingdom, renal disease secondary to diabetes is the most frequently made primary renal diagnosis (Farrington e*t al.* 2006). Studies have shown that diabetes is the main cause for the preponderance of CKD in 18% to 30% of cases (Dreyer *et al*. 2009; New *et al.* 2007; Middleton *et al.* 2006). In addition, CKD is considered an independent risk factor for cardiac disease as well as for the evolution of established renal failure. According to Foley *et al.* (2005), atherosclerotic vascular disease increased the likelihood of developing chronic kidney disease by 1.5, whereas congestive cardiac failure increased the likelihood of developing CKD almost twofold. Once a patient reaches ESRD, his/her quality of

life becomes invariably poor and life expectancy considerably shortened (Centres for Disease Control and Prevention 2010).

ESRD is a serious condition affecting a large part of the population and, as such, it represents a considerable financial burden for the health sector. Total Medicare ESRD expenditures in the USA was 29 billion dollars in 2009 (USRDS 2011). Programme budgeting analysis by the department of health estimated in England, the total NHS expenditure on kidney care, including CKD, at £1.71 billion in 2009–10 (Department of Health 2012). The condition is made worse by the fact that a proportion of patients (30%) are referred late to the kidney specialist, increasing the risk of mortality and morbidity (NICE Guidelines 2008). Worldwide the prevalence and incidence of ESRD is growing continuously. CKD places a considerable demand on medical resources around the world. Between 2008 and 2009, the number of people in England over 18 years of age who were diagnosed with chronic kidney disease, stage 3-5, was 1.7 million, which represents 4.1% of the adult population (NHS Kidney Care 2010). According to the National Institute of Diabetes, Digestive, and Kidney Diseases (2003), diabetic nephropathy represents the major cause for the growing preponderance of ESRD. Among the other factors contributing to the aggravation of ESRD are hypertension, glomerulonephritis, polycystic kidney disease, smoking, and obesity (NHS Kidney Care 2010).

The principal feature of chronic kidney failure is the persistently abnormal glomerular filtration rate, which is associated with a sudden and constant increase in the amount of urea and creatinine. This can lead to serious complications, such as volume overload, hyperkalaemia, and metabolic acidosis (Scottish Intercollegiate

Guidelines Network 2008). Thus, it can be said that chronic kidney failure is a gradually developing disease triggered by a number of factors, resulting in varying severity of kidney damage.

Chronic kidney failure features are common to progressive disease and can be observed histologically as interstitial fibrosis, glomerulosclerosis, and destruction of kidney cells. Three main causes of kidney failure have been identified: a decline in renal blood flow, determined in 40-70% of cases by pre-renal factors (Kaufman *et al.* 1991; Hou *et al.* 1983), damage to the parenchymal kidney tissue, brought about in 10-50% of cases by internal kidney problems, and obstructed urine flow, determined in 10% of cases by post-renal factors (Liano and Pascual 1996).

2.1.2 Aetiology and Pathological Changes

2.1.2.1 Pre-renal Causes

Principal pre-renal causes of renal failure are hypovolaemia, renal hypoperfusion, hypotension and oedematous state such as cardiac failure (Table 1). The renal blood flow and glomerular filtration rate is maintained across different mean arterial pressure due to modifications in pre-glomerular and post-glomerular arteriolar resistance. If the arterial pressure drops below 70 mmHg, there is a decline in the GFR and the renal auto-regulation is affected. As explained by Madala (2007), the latter depends on a number of elements, including pre glomerular arteriolar vasodilatation, facilitated by nitric oxide and prostaglandins, and post glomerular arteriolar vasoconstriction, facilitated by angiotensin II peptide. There are some drugs, which can inhibit the mediators, such as selective cyclooxygenase 2 inhibitors

or non-steroidal anti-inflammatory drugs, as well as angiotensin converting enzyme blockers or angiotensin II receptor inhibitors. In certain cases, such inhibitors can determine pre-renal acute renal failure (Wolf and Ritz 2005). The patients that can be severely affected by this condition are those with ischaemic heart disease, pre-existing CKD and renal hypo perfusion, which is brought about by volume depletion, low blood pressure, or stenosis of the renal artery (Levey *et al*. 2003).

Table 1. Pre-renal Causes of Renal Failure (Waikar *et al*. 2008; Hilton 2006)

Hypovolaemia
• Severe Blood Loss
• Severe Dehydration (vomiting, diarrhoea, inappropriate diuresis, burns)
Renal hypo perfusion
• Non-steroidal anti-inflammatory drugs
• Angiotensin converting enzyme inhibitors
• Abdominal aortic aneurysm
• Renal artery stenosis/occlusion
• Hepatorenal syndrome
Hypotension
• Cardiogenic shock
• Severe Infection (Sepsis), Anaphylaxis
Oedematous states
• Cardiac failure
• Pancreatitis, Liver cirrhosis
• Nephrotic syndrome

Pre-renal kidney failure occurs when a sudden reduction in blood flow to the kidney (renal hypoperfusion) causes a loss of kidney function. In pre-renal kidney failure, there are no intrinsic abnormalities with the kidney itself.

2.1.2.2 Intrinsic Renal Causes

Diseases, which affect glomeruli, renal tubules, interstitium, or vasculature, can trigger intrinsic renal failure (Table 2). Its morphological appearance is characterised by fibrosis and destruction of normal renal cells generally as a result of apoptosis and invasion of monocytes and/or macrophages, which are the outcome of the interaction between vaso-active substances, such as growth factors and cytokines (Singh *et al*. 2010). However, the main determinant of intrinsic acute renal failure is acute tubular necrosis, generated by the same pathophysiological processes, which cause pre-renal hypo perfusion. Among the various factors, which can lead to the development of intrinsic acute renal failure, the most frequently encountered is sepsis, which develops as a result of hospital acquired infection and can be associated with the multiple organ dysfunctions (Mehta *et al.* 2004). Post-surgery acute tubular necrosis is a cause of hospital acquired acute kidney failure, which develops in 25% of cases and is generally determined by pre-renal factors (Carmichael and Carmichael 2003). Acute radio contrast nephropathy is another condition, which triggers the development of hospital acquired acute renal failure (Lameire *et al.* 2005). Clinically, radio contrast-induced nephropathy is defined as a sudden decline in renal function after radio contrast administration during image-guided cardiology and radiology procedures (Weisbord and Palevsky 2005). Studies showed evidence of acute tubular necrosis secondary to radio contrast administration (Detrenis *et al*. 2005; Persson *et al*. 2005). Acute tubular necrosis is caused by renal vasoconstriction resulting in medullary hypoxia and due to direct result of the cytotoxic effects of the contrast agents (Heyman *et al*, 2005; Pflueger *et al*. 2000).

Table 2. Causes of Intrinsic Renal Failure (Jha *et al*. 2013; Hilton 2006)

Glomerular Disease
• Inflammatory: post-infectious glomerulonephritis, henoch schonlein purpura, systemic lupus erythematosus, glomerulonephritis,
• Thrombotic: disseminated intravascular coagulopathy, thrombotic microangiopathy
Interstitial Nephritis
• Drug induced: non-steroidal anti-inflammatory drugs (NSAID), antibiotics
• Infiltrative lymphoma
• Sarcoidosis
• Tuberculosis
• HIV associated nephropathy
• Hepatitis B and C viruses
• Pyelonephritis
Vascular
• Vasculitis
• Polyarteritis Nodosa
• Thrombotic Microangiopathy
• Cholesterol Emboli
• Renal Artery or Vein thrombosis
Tubular Injury
• Prolonged renal hypoperfusion
• Drugs (such as aminoglycosides), pigments (such as myoglobin), heavy metals (such as cisplatinum)
• Hypercalcaemia
• Crystals: urate, oxalate

Intrinsic acute renal failure may be caused by diseases affecting the glomeruli, renal tubules, interstitium, or vasculature.

2.1.2.3 Post-renal Causes

Obstructive nephropathy is a rare form of kidney failure but, nonetheless, it needs to be identified to ensure an efficient treatment, which can improve kidney function or even restore it entirely (Table 3). Patients who are prone to develop this condition are men of an advanced age with prostate disease, as well as individuals with abdominal malignancy, especially the pelvis (Haynes and Winearls 2010). Vesico ureteric reflex accounts for renal failure in young adults. Vesico ureteric junction obstruction is more common in males than in females and affects the left ureter more than on the right (Lopez-Nova *et al.* 2010). Upon elimination of the obstruction, patients may experience diuresis, and they have to be closely monitored and provided with sufficient fluids to prevent volume depletion.

Table 3. Causes of Post Renal Failure (Lopez-Nova *et al.* 2010)

Intrinsic
• Ureteric (intra-luminal) stone
• Blood clots in the ureter or urethra
• Papillary necrosis
• Intra-mural urethral stricture
• Bladder tumour
Extrinsic
• Pelvic malignancy (such as Prostatic hyperplasia, cervix)
• Retroperitoneal fibrosis

Post renal failure is sometimes referred to as obstructive renal failure, since it is often caused by something blocking elimination of urine produced by the kidneys.

2.1.3 Predisposing Factors

There are multiple factors that may increase the risk of developing chronic kidney disease include

2.1.3.1 Smoking

Studies have revealed that smoking is a factor contributing to advancement in diabetic nephropathy (Chuahirun and Wesson 2002), primary renal disease (Orth *et al.* 1998), and severe hypertension (Regalado *et al*. 2000). In addition, it is a risk factor for the presence of an excess of serum proteins in the urine, irrespective of the existence of diabetes and hypertension, and can contribute to the advancement of the disease (Halimi *et al.* 2000). Orth (2000) also discovered that smokers suffering from diabetes, whether or not they are dependent on insulin, are more prone to develop kidney disease with an increased rate of development and progression towards end stage kidney failure. Smokers that have a high blood pressure can develop albuminuria (Horner *et al.* 1996; Mimran *et al.* 1994) and may suffer deterioration of kidney function (Regalado *et al*. 2000). Ejerblad *et al.* (2004) conducted a nationwide-population based study in Sweden and discovered that current or former smokers are likely to develop chronic kidney failure. Their results contraindicated the results of earlier studies (Perry *et al.* 1995; Nuyts *et al.* 1995) which did not find evidence regarding an association between renal disease and smoking.

The odds ratio was directly proportional to how often and for how long patients smoked. To calculate a ‘pack year’, the number of cigarette packs smoked daily was multiplied by the number of years that a person has smoked for. The likelihood of

developing chronic kidney disease increased exponentially if a person accumulated over 15 pack years (between 16 to 30 pack years equalled 1.32; more than 30 pack years equalled 1.52) (Ejerblad *et al.* 2004).

2.1.3.2 Asians and African American Descent

There is a higher prevalence of diabetes mellitus in south Asian populations (Ali *et al.* 2013; Stewart *et al.* 2006). Li *et al*. (2004) concluded that the ethnical difference in the incidence of CKD might partly be due to a higher prevalence of primary causal diseases of CKD such as diabetes. Established renal failure as a complication of diabetes is 10 times greater in South Asians than in Caucasians (Jain *et al*. 2008). A recent study involving 1810 patients was conducted in one of the most ethnically diverse city (Birmingham) in the UK where the incidence of renal replacement therapy for south Asian and Black groups was reported to be, respectively, 1.88 and 2.16 times greater than for White patients (Lambie *et al*. 2008).

A study was carried out by Klag *et al.* (1997) on a group of men with untreated hypertension but without history of diabetes, who had registered in the Multiple Risk Factor Intervention Trial (MRFIT). The study results revealed that black individuals were more prone to develop end-stage renal disease, without the influence of other causes. Another study (Feehally 2005) revealed that African Americans reach end-stage kidney disease at younger ages than white people (mean age 57 versus 63 years respectively). The examination of the basic features of the modification of diet in renal disease carried out by Hunsicker *et al.* (1997) discovered an association between black ancestry and a more rapid GFR decrease. This accelerated advancement of disease in people of black descent has been attributed to two main

factors; the social environment and genetic inheritance. Merkin *et al.* (2005) conducted a study on the connection between these two factors and found that white males and black females living in a disadvantaged area or low socioeconomic status were more likely to have a rapid progression of chronic kidney disease than if they lived in a more affluent area. In contrast, the analysis of white females and black males did not reveal any relation between the social environment and predisposition towards chronic kidney disease. However, this study had a number of drawbacks, since it provided insufficient data on sampling methods and attrition proportion.

2.1.3.3 Diabetes Mellitus

According to Bakris (2011) and Van Buren and Toto (2011), the incidence rate of diabetic nephropathy has experienced a significant growth in recent years and it is currently the main determinant of ESRD on a global scale. In 40% of cases, it also has an influence on the development of CKD among adults suffering from type 2 diabetes. This co-morbidity can lead to disability, causing a strain on the health care budget, with annual estimates of $23 billion in the United States (Go *et al.* 2004). The 2009 annual report published by the USRDS indicated the preponderance of each stage of CKD associated with type 2 diabetes; stages one to five had the following prevalence percentages: 8.9%, 12.8%, 19.4% and 2.7% for the latter two combined stage four and five respectively. Individuals suffering from type 1 diabetes have a 25% chance of developing chronic kidney disease (Alleyn *et al.* 2010; Centre for Disease Control and Prevention 2007). By analysing a series of factors, such as age, family background, earnings, hypertension, serum cholesterol, and ischaemic

heart disease, Brancati *et al.* (1997) observed that men suffering from diabetes have a greater predisposition towards ESRD, independent of any diabetic complications.

The development of diabetic CKD has a number of causes. As explained by Pyram *et al.* (2012), in the early stages of development, adaptive hyper-filtration generates longstanding functional deterioration of the nephrons. Type 1 and 2 diabetes intervention trials have pointed towards the influence of glycaemia in this process. Analyses showed that improved glycaemic levels determined a decrease in the advancement rate of albuminuria (UKPDS 1998).

2.1.3.4 Male Gender

A number of researchers (Zhang and Rothenbacher 2008; Coggins *et al.* 1998; Jungers *et al.* 1995; Schieppati *et al.* 1993; Gabow *et al.* 1992; Rekola, *et al*. 1991) have argued that kidney diseases, unaccompanied by diabetes, are more likely to develop at an accelerated pace in men. Nonetheless, these studies do not follow a similar design and methodology. What is more, they have failed to indicate that the gender factor is not associated with other factors, such as proteinuria, hypertension, and smoking history. Several studies (Seliger *et al.* 2001; Zdunek*et al.* 2001; Miller *et al*. 1999a) have focused on the different mechanisms involved, as well as the increased reaction to angiotensin II in men and the capability of oestradiol to overturn transforming growth factor-beta1 (TGF β1) mediated fibrogenesis. According to Negulescu *et al.* (2002), this phenomenon contributes to the positive influence of the female gender on the progression of CKD. Hyperuricaemia has also been associated with renal dysfunction and CKD. Li *et al*. (2012) suggested that the association of hyperuricaemia with CKD is significantly stronger in males than that

in females. A potential explanation for this relationship of hyperuricaemia with the prevalence of CKD may lie in the fact that in females oestrogen increases the excretion of uric acid in the urine, thus reducing the concentration of uric acid in blood plasma (Mok *et al*. 2012; Johnson and Rideous 2004), and the possible mechanism for the gender difference in the hyperuricaemia with the progression of CKD.

2.1.3.5 Hyperlipidaemia

Among the implications of chronic kidney failure is an increase in the levels of triglyceride, oxidized low-density lipoprotein, and depleted Apo lipoprotein. Vaziri *et al*. (2001) highlighted the fact that kidney failure can contribute to the development of hyperlipidaemia by decreasing the activity of the enzyme lecithin, namely, the cholesterol acyltransferase in the liver and its action in the plasma.

The experiments conducted by Joles *et al.* (2000) have revealed that both hypercholesterolaemia and hypertriglyceridaemia have the ability to cause proteinuria and tubulointerstitial injury; the development rate can be decreased by treatments which target the levels of lipids (Oda and Keane 1997). Such conditions can cause damage by overproduction of the reactive oxygen species including superoxide anion (O^{-2}), hydroxyl radicals (HO^{-}), lipid radicals (oxLDL) peroxynitrite ($ON\text{-}OO^{-}$) and nitric oxide (NO^{-}), modulation of mesangial growth and proliferation, suppressing the production of nitric oxide, enabling infiltration of monocytes and activating growth factor and cytokine release (Park and Oh 2011; Stapleton *et al*. 2010; Stevenson *et al*. 2001).

In humans, a raised level of serum lipid is associated with the occurrence of kidney insufficiency and advancement of existing kidney disease (Hunsicker *et al.* 1997). Nevertheless, it is still uncertain whether a clear causal relationship exists, particularly as the element(s) of the dyslipidaemic milieu that control the advancement of the disease are largely unknown (Muntner *et al.* 2000). A number of potential contestants have been proposed, including increase in the levels of cholesterol, low and high density lipoprotein, high levels of triglyceride, and Apo lipoprotein B consisting of lipoproteins (Samuelsson *et al*. 1998).

2.1.3.6 Recreational Drug Use

Perneger *et al*. (2001) and Norris *et al.* (2001) have indicated that there is an association between the use of heroin and other opiates as well as of cocaine, and the likelihood of developing ESRD. Cocaine has the potential to aggravate hypertensive nephrosclerosis through development of renal ischemia. It has not yet been determined if there is a causal connection between heroin and other opiates and the predisposition towards the disease or if they are stand-in markers for other factors.

2.2 Clinical Manifestations

Chronic kidney disease is usually silent. According to Haynes and Winearls (2010), chronic kidney disease only reveals symptoms later on, typically when end stage kidney disease is forthcoming. Although every patient may experience these symptoms in various ways, the section below covers the most widespread chronic renal failure symptoms.

- Poor appetite
- Vomiting
- Bone pain
- Headache
- Insomnia
- Itching
- Dry skin
- Malaise
- Fatigue with light activity
- Muscle cramps
- High urine output or no urine output
- Recurrent urinary tract infections
- Urinary incontinence
- Pale skin
- Bad breath
- Hearing deficit
- Detectable abdominal mass
- Tissue swelling
- Irritability
- Poor muscle tone
- Change in mental alertness
- Metallic taste in mouth

If the kidney function declines to stage 4 or 5 then various other problems may develop such as anaemia and an imbalance of calcium, phosphate and other chemicals in the bloodstream. These can cause various symptoms, such as tiredness due to anaemia, and bone thinning or fractures due to calcium and phosphate imbalance. End-stage renal failure (stage 5) is eventually fatal unless treated.

2.3 Diagnosis of Kidney Failure

Aetiology and laboratory test results are the conventional foundations for determining the presence of CKD. Patient's history, a physical examination, and pathology test results of a particular individual are helpful in providing a differential diagnosis of the disease (Table 4).

Tomson and Bailey (2011) and Haynes and Winearls (2010) provided a list of the diagnostics used in identifying renal failure (this is after a physical examination, including blood pressure measurement, is completed along with an abdominal examination to identify a distended bladder or enlarged kidneys and a full medical

history is provided). The diagnostics are: 1) urine analysis which looks for proteinuria, albuminuria and haematuria; 2) blood tests to define electrolyte levels, kidney function and blood cell counts; 3) a renal ultrasound used to examine the kidneys and to identify kidney stones, cysts, masses or other irregularities; 4) a renal biopsy which is necessary to identify whether there are any abnormal or cancer cells; 5) immunological exams which are used to determine whether a patient is suffering from vasculitis, myeloma or primary amyloid (these tests are more useful in dealing with AKI and rarely find the origins of chronic kidney disease); 6) a CT scan which is able to present images of the kidneys.

Table 4. Diagnosis of Chronic Kidney Disease (K/DOQI. 2002)

	Diagnosis
Review of systems	
Symptoms during urination	Usually suggest disorders of the urinary tract, such as infection, obstruction, or stones
Recent infections	May suggest post infectious glomerulonephritis or HIV-associated nephropathy
Skin rash or arthritis	Suggests autoimmune disease, such as systemic lupus erythematosus or cryoglobulinemia.
Risk factors for parentally transmitted disease	May suggest HIV, hepatitis B, or hepatitis C and associated kidney diseases
Chronic diseases	
Heart failure, cirrhosis, or gastrointestinal fluid losses	Usually suggest reduced kidney perfusion (prerenal factors).
Diabetes†	As a cause of chronic kidney disease: Diabetic kidney disease usually follows a typical clinical course after onset, first with micro albuminuria, followed by clinical proteinuria, hypertension, and declining GFR*
Hypertension†	As a cause of CKD: Hypertensive nephrosclerosis is usually characterized by severely elevated blood pressure readings over a long period, with associated end-organ damage in addition to kidney disease. Recent worsening of hypertension, in association with findings of diffuse atherosclerosis, suggests renal artery disease due to atherosclerosis.

	Diagnosis
Medical history	
Findings from previous routine examinations	May reveal a history of hypertension or proteinuria during childhood; during pregnancy; or on examinations for school, military service, or insurance
Previous urologic evaluations	Details may disclose radiologic abnormalities associated with kidney disease
Predominant male susceptibility	Suggests a sex-linked recessive disease, such as the Alport syndrome.
Less frequent than every generation	Suggests an autosomal recessive disease, such as medullary cystic kidney disease or autosomal recessive polycystic kidney disease

* GFR glomerular filtration rate, † extremely common in elderly patients and often nonspecific. CKD is diagnosed through patient's medical history, risk factors and clinical presentation. Specific diseases are associated with specific risk factors and are manifested by specific clinical presentations.

Chronic kidney disease reveals symptoms only in the late phases; as such, it is generally diagnosed by analysing the serum creatinine or testing of protein in the urine. A significant proportion of CKD could not be recognized, as serum creatinine cannot identify increasing kidney failure in women or old people due to low sensitivity (Johnson 2005a; Drey *et al.* 2003). Guidelines have been introduced in clinical practice in Great Britain based on the four elements of the Modification of Diet in Renal Disease (MDRD) equation, a simple, rapid, and reliable means of assessing kidney function and albumin creatinine ratio (NICE Guideline 2008; Johnson 2005b). Furthermore, it is hoped that the use of the estimated Glomerular Filtration Rate (eGFR), as well as the preservation of patient's records with CKD stages 3 to 5 (Quality and Outcomes Framework 2003), will lead to a more efficient diagnosis of CKD and improvement of treatment methods. The categorization of chronic kidney disease employed by the National Service Framework (NSF) is the five-stage categorization proposed by NKF-KDOQIb (2006). According to this, the

late stages of CKD can be determined by using the eGFR measurements, whilst stages 1 and 2 are identified by the constant presence of proteinuria, albuminuria or structural abnormalities or haematuria. As shown in Table 5, NICE Guidelines (2008) adjusted this categorization by creating two subcategories of stage 3, stage 3a and stage 3b. An eGFR level of 60-89 ml/min/1.73m^2 which is not associated with any of the above mentioned criteria for the different stages of CKD should be taken as an indication that the patient does not suffer from CKD.

Table 5. Stages of Chronic Kidney Disease (NICE Guideline 2008)

Stage	***eGFR(ml/min/1.73 m^2)***	***Description***
1	≥ 90	Normal or increased GFR, with other evidence of kidney damage
2	60-89	Slight decrease in GFR, with other evidence of kidney damage
3A	45-59	Moderate decrease in GFR, with or without other evidence of kidney damage
3B	30-44	
4	15-29	Severe decrease in GFR, with or without other evidence of kidney damage
5	< 15	Established renal failure

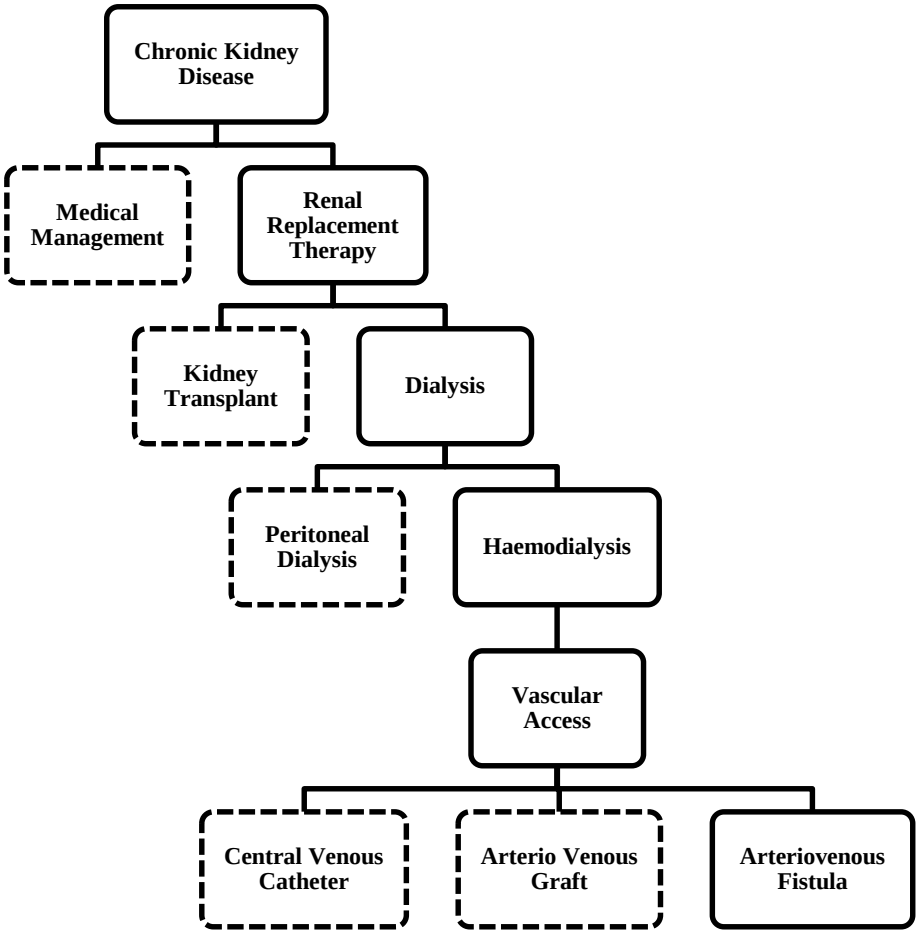
Glomerular filtration rate (GFR) is the best measure of kidney function. The GFR is the number used to classify stage of kidney disease. There are five stages of CKD however kidney function is normal in Stage 1, and minimally reduced in Stage 2.

2.4 Management of Chronic Kidney Disease

The objective of the treatment of CKD is to take into consideration patient requirements and ensure a positive result. There are currently two treatment options for individuals who suffer from CKD, medical management or Renal Replacement Therapy (RRT) (Figure 2). UK Renal Association guidelines (2011) recommend that all patients with stage 5 CKD, who are capable of withstanding such an extensive surgical procedure and can adapt to chronic immunosuppression, should have a

kidney transplant. Ideally, the kidney should be taken from a living donor, if a suitable one exists. However, the waiting lists for living donor transplant are usually large, reaching 7,235 in the United Kingdom, a number that increases annually by almost 8% (NICE Guideline 2008). The real number of patients requiring a kidney is believed to be even higher, but clinicians do not record all of them, as the probability of them receiving a kidney is rather low.

Figure 2. Management of Chronic Kidney Disease



The stepwise management plan of chronic kidney disease. Stage 1-4 CKD can be treated by medical management. In stage 5 (End Stage Kidney Disease) RRT is indicated. The decision whether to have dialysis or a kidney transplant depends on multiple factors such as hemodynamic stability and availability of donors. There are two types of dialysis – haemodialysis and peritoneal dialysis. In order to obtain haemodialysis, patients require a vascular access.

After kidney transplant, haemodialysis and peritoneal dialysis are the best active treatment options for people with ESRD (Dhoul *et al*. 2011). Korevaar *et al.* (2003) conducted a randomised controlled trial examining the differences in treatment outcome of haemodialysis and peritoneal dialysis and discovered that there were no considerable distinctions, both methods exhibiting a two year quality adjusted life or five-year mortality. Peritoneal dialysis is a treatment, which patients can carry out by themselves at home. In contrast, haemodialysis treatment generally requires patients to go to a medical centre, normally three times a week. Although a small proportion of patients undertake home haemodialysis.

2.4.1 Medical Management

The goal of treatment for chronic kidney disease is to treat the underlying cause, control signs and symptoms, reduce complications, and slow further damage to the kidneys (Haynes and Winearls 2010). One of the most important parts of treatment is to control the disease that is causing kidney damage such as diabetes or hypertension. The main focus of CKD management includes

- Life style modification
- Lowering blood pressure
- Tight glycaemic control
- Reducing proteinuria
- Lowering blood cholesterol
- Management of anaemia
- Management of mineral and bone disorders

2.4.2 Renal Replacement Therapy (RRT)

2.4.2.1 Introduction

There are a number of factors, which have to be taken into account when deciding the usage of RRT in patients suffering from ESRD, such as evaluation of electrolyte and acid-base balance, intravascular volume, uraemia, dietary needs, haemodynamic status, urine output, and the development of the disease in each individual case. The benefits of RRT have to be compared with the possible hazards of surgical intervention, such as bleeding caused by anticoagulants, as well as all types of complications that accompany the central venous access. Pannu *et al.* (2008) have argued that, in the case of seriously ill patients, if they have developed metabolic acidosis, hypervolemia, and hyperkalaemia, which are unresponsive to any type of treatment, RRT is the only viable solution. Despite the fact that, theoretically, there are advantages to commencing RRT early on, there is insufficient information about when is the right time for patients suffering from acute renal failure to begin dialysis (Liu *et al.* 2006). John *et al.* (2004) and Drey *et al.* (2003) have also drawn attention to the fact that many types of chronic kidney disease are still unknown, because the serum creatinine fails to identify decreasing kidney function, especially in women and old individuals. According to the Quality and Outcomes Framework (2003), the diagnosis of chronic kidney disease and improvement of treatments will be mediated by the introduction of eGFR reporting, as well as by the preservation of patient records required of all UK general practitioners.

As noted by Levin *et al.* (2008), many patients suffering from chronic kidney disease die before they reach ESRD. Nevertheless, the stabilizing prevalence rate of RRT

cannot be explained by any prognostic for growing mortality among patients with CKD (USRDS 2008). Gallego *et al.* (2003) proposed that the limited use of RRT as a result of patients being referred to kidney specialists late or not at all can be considered an additional cause for the stagnation in prevalence. This hypothesis is not supported by the statistics, which have revealed that the prevalence rate among patients of advanced age, who have an increased likelihood of being affected, has exhibited a constant rise. The growing proportion of individuals suffering from chronic kidney disease has considerable repercussions for both kidney specialists and primary care, from a resource point of view. The existing United Kingdom guidelines for CKD in adults suggest that every individual with stage 4 CKD should have a discussion with a kidney specialist (Chronic kidney disease in adults: UK guidelines 2006). In reality, it may not be possible or even necessary for all patients to have these consultations. As a result, the creation of a risk assessment predictive model is warranted, in order to enable doctors to decide which cases are most urgent and arrange consultations with nephrologists for them.

2.4.2.2 Function and Types of RRT

Kidney disease secondary to diabetes is the commonest single cause of ESRD and accounts for 24% of incident diagnoses of patients starting RRT in the UK (Byrne *et al*. 2010). Variations in RRT incidence may reflect the quality of chronic disease management in diabetes and high blood pressure (Udayaraj *et al*. 2010; Kramer *et al*. 2009).

The dialysis-based treatment of ESRD patients is aimed towards preserving fluid and electrolyte, acid-base and solute homeostasis, safeguarding the kidney from

additional damage, stimulating restoration of kidney function and enabling the activity of other support measures, such as nutrition. When making a decision related to dialysis treatment, it should be taken into account that different methods of dialysis have different operative mechanisms through which they provide kidney support. One such example is the fact that dialysis is largely viewed as a method to remove solute and fluids, as these are the main options utilized for ESRD patients.

The period 1997-2006 witnessed a substantial increase in the survival rate of patients who underwent dialysis or kidney transplant. Kramer *et al.* (2009) argued that, in addition to the technical advancements in renal replacement therapy, the growing public awareness of the necessity of identifying and treating chronic kidney disease at an early stage meant that patients beginning to receive RRT were in a far better physical condition than before, which also contributed to the increase in the survival rate (Arora *et al*. 1999; Eadington 1996; Jungers *et al*. 1993). Some people are more suitable to one type of dialysis than the other as the choice of RRT (kidney transplant, haemodialysis and peritoneal dialysis) depends on multiple factors, including the primary need underlying indication such as acute or chronic kidney failure, hemodynamic stability, other comorbid diseases, availability of local expertise, and patient preference and capability for home dialysis. However, not all renal units in the UK are able to offer patient choice because in many areas, stretched dialysis resources may limit the availability of haemodialysis. Patients receiving peritoneal dialysis have a greater chance to develop infections than the general population, because of risk factors such as immune deficit and cutaneous access point (Mekki *et al.* 2010). A case control study (Ridao Curty *et al*. 2014) of 644 patients was conducted in the RRT outpatient centre for 29-month period. The study

results concluded that peritoneal dialysis is the treatment with greater risk of infection and mortality, followed by catheter haemodialysis. The lowest risk of infection and mortality was observed in the arteriovenous fistula haemodialysis group. Most studies suggest that outcomes of patients treated by PD and HD are similar (Gokal *et al*. 1999), and that patients who start with PD first may even have better control on kidney function (Heaf *et al*. 2002). However, other studies demonstrated a higher mortality with PD starting from the second year of treatment, and suggested possible survival benefits of a timely change over from PD to HD (Jaar *et al*. 2005). The higher PD mortality probably relates to sepsis and peritoneum exhaustion (Sinangil *et al*. 2013; USRDS 2005). Peritoneal exhaustion (peritoneal sclerosis) is an extensive thickening of the peritoneal membrane due to fibrous tissue and new vessel formation, usually as a result of long-term PD (Nakayama 2005). Among the suggested aetiologies are the severe or recurrent peritonitis, bacterial endotoxin and inflammatory or foreign body response to the peritoneal catheter (Kawanishi and Moriishi 2007; Eltoum *et al.* 2006).

Dialysis and transplantation provide alternative ways of taking over the work of patients failed kidneys. Transplantation of kidney involves the replacement of an abnormal kidney of a recipient with a better functioning kidney of the donor. The most efficient form of therapy for ESRD patients is a kidney transplant.

2.4.3 Kidney Transplantation

Kidney transplantation is the treatment of choice for selected patients with ESRD (Suthanthiran and Strom 1994). However, there is a shortage of donated organs and a growing wait-list for transplantation (Whalen *et al*. 2012; Xue *et al*. 2001). Many

people who are candidates for kidney transplantation are put on a transplant waiting list and require dialysis until an organ is available. A successful kidney transplant improves the quality of life and reduces the mortality risk for most patients when compared with maintenance dialysis (Schnuelle *et al*. 1998; Portet *et al*. 1993; Ojo *et al*. 1994).

Kidney transplant is a much more effective treatment than dialysis for removing the symptoms of kidney failure. Among the 46,164 ESRD patients on the kidney transplant waiting list in the United States during the period 1991-1997, those who received a transplant were 68% less likely to die than those who did not receive a transplant, in the subsequent three years (Wolfe *et al.* 1999). The overall survival rate increased by ten years, and in the younger age group this increased to 17 years compared to those on a transplant waiting list. The escalation in the survival rate was observed equally in males and females, and was particularly high in patients suffering from diabetes. A large-scale longitudinal study of survival and mortality risk study in 1736 adult patients carried out in Scotland revealed similar results, study results concluded that there is a substantial long-term survival advantage for transplantation compared with dialysis (Oniscu *et al.* 2005).

2.4.4 Peritoneal Dialysis

2.4.4.1 Introduction

Peritoneal dialysis represents a method of RRT, which counters the role of HD and transplant in the treatment of ESRD. The method helps to eliminate the nitrogenous waste products and fluids from the body through a catheter inserted into the

peritoneal cavity. As it is a simple and straightforward method, patients can carry it out themselves at home after undertaking a short training session. PD does not usually necessitate any special equipment, so it can be readily adapted to the patient's lifestyle. In spite of this, it does require a patient to have a lot of storage space for the dialysis fluid.

Peppelenbosch *et al.* (2008) indicated the benefits of peritoneal dialysis in contrast to haemodialysis, such as enhanced quality of life as a result of patient mobility and autonomy, ease of use, preservation of residual kidney function, as well as a low mortality rate in the years immediately following the start of the treatment. However, patients initially improve on PD, and later tend to deteriorate because of volume expansion, coinciding with further loss of residual renal function (Ortega and Materson 2011).

2.4.4.2 Complications of Peritoneal Dialysis

Ortega and Materson (2011) have indicated hypertension to be an important consequence of peritoneal dialysis in 29% to 80% of patients, particularly as cardiac disease is the most frequent cause of mortality among ESRD population. Furthermore, capacity overload also occurs because of the introduction of fluids in the body and destruction of residual kidney function. In rare cases, long-term PD can lead to the development of massive hydrothorax, which is a severe complication. It can develop at any moment during the therapy and can cause severe dyspnoea (Nomoto *et al.* 1989).

Despite substantial advances in PD as a renal replacement therapy, PD-related infections including peritonitis and exit site infection remains an important determinant of disease and death. Peritonitis represents the serious complication of PD (Piraino 1998), being not only life threatening, but also the leading risk factor for disease in patients undergoing PD and is the major cause of hospitalization, catheter loss, and technique failure (Wang *et al.* 2011; Fried *et al.* 1996).

Catheter-related mechanical complications, which include malposition, kinking, and entrapment of the catheter, may prevent adequate drainage of the dialysate (Stuart *et al*. 2009). Peritoneal dialysis patients have increased intra peritoneal pressure due to the presence of fill volume in the peritoneal cavity, resulted in the risk of abdominal wall complications, such as hernias and peritoneal leaks (Peso *et al*. 2003). After a number of years, the peritoneal membrane also becomes less efficient in dialysis due to peritoneal sclerosis and fibrosis. Long-term systemic exposure of the peritoneal cavity to dialysis solutions results into peritoneal membrane structural and functional alterations over time and eventually to technique failure expressed clinically as ultrafiltration failure and reduced solute clearance (Fourtounas 2011).

2.4.5 Haemodialysis

2.4.5.1 Introduction

Progressive and permanent renal failure is most frequently treated with haemodialysis. Since 2009, the number of patients receiving home HD has increased by 23%, from 636 to 780 patients with median age of 66 years (UK renal registry report 2011). Haemodialysis has been used to treat renal failure since the 1960s

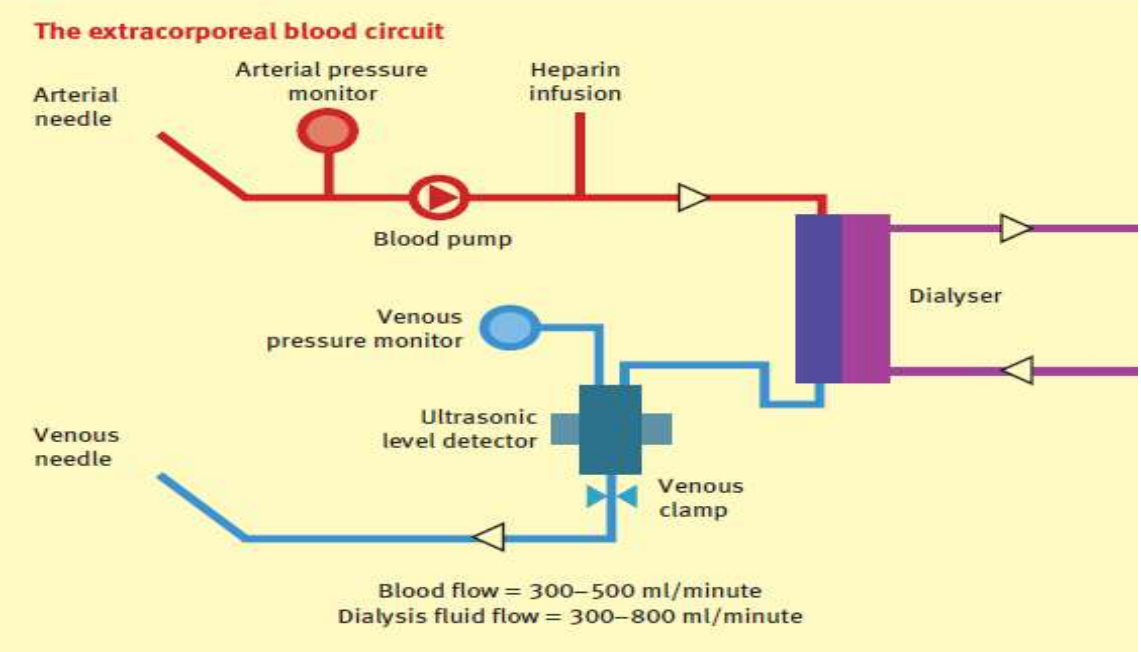
(Grassmann *et al.* 2006). RRT with haemodialysis does not provide true replacement of renal function. However, by removing waste solutes, excess body water and restoring biochemical and acid-base balance, haemodialysis has considerably improved the morbidity and mortality of ESRD patients.

The first haemodialysis performed in a human was by Haas in 1924 (Haas 1925; Paskalev 2001). Twenty years later Willem Kolff provide a primitive form of vascular access, establishing effective anticoagulation and producing reliable equipment for widespread use when he created the rotating drum kidney in 1943 (Kolff and Berk 1944; Konner 2005).

2.4.5.2 Mechanism of Haemodialysis

The current haemodialysis machine bears little resemblance to that devised by Kolff in 1943 although the design adheres to similar principles (Konner 2005; Kolff and Berk 1944). This centres on removing blood from the intravascular compartment, passing it through an extracorporeal circuit into a dialyser and removing waste solutes and excess water by exposure to conditions that promote diffusion, convection, and movement in response to hydrostatic pressure gradients. Dialysed blood is then returned to the patient through the venous system. The volume of plasma cleared of solute per unit time by dialysis is expressed as the solute clearance. Diffusion is the predominant method by which solute clearance from plasma is achieved by haemodialysis. The process of diffusion is dependent upon blood from the extracorporeal circuit flowing through the dialyser, a collection of microfilament fibres bathed in dialysate fluid, which circulates in the opposing direction to blood flow (Figure 3).

Figure 3. Mechanism of Haemodialysis (Pandya and Farrington 2003)



Blood is withdrawn from the fistula via the needle by a peristaltic pump, circulated through the dialyser, and returned to the fistula downstream through the needle. Heparin is infused downstream from the blood pump.

These conditions are favourable to the rapid diffusion of solutes through pores within the microfilament fibres, down a concentration gradient from blood to dialysate or vice-versa. The rate of diffusion varies with the degree of concentration gradient between compartments, the surface area of the microfilament membrane, the number and size of pores within the membrane, the molecular size of the solute and the relative flow rates of both extracorporeal blood and dialysate (Pandya and Farrington 2003).

It can be seen that key determinants in the success of haemodialysis are the characteristics of the selectively permeable membranes used to form the microfilament tubes within dialyser units. Membranes may now be classified by the type of material used in their manufacture (synthetic, cellulose and substituted

cellulose), their capacity, surface area, ultrafiltration coefficient, flux and in some cases, their ability to be reused (NKF-KDOQIb 2006).

2.4.5.3 Functional Outcomes of Haemodialysis

A high level of serum albumin has been considered as a positive measure of survival prediction in patients receiving dialysis due to the fact that it is an indicator of improved nutrition and reduced inflammatory burden (Avram *et al.* 1995). Block *et al.* (1998) have demonstrated that a reduced concentration of calcium phosphate is also a measure of increased survival rate as it is an indicator of efficient treatment of bone disease. Renal anaemia, reflected by low haemoglobin levels (Locatelli *et al.* 2004), and low dialysis doses (Held *et al*. 1996) is associated with unsatisfactory and poor outcomes of haemodialysis (Elseviers and van Wadeghem 2003).

The DOPPS have demonstrated that arteriovenous fistula is exceeding in its benefits regarding the provision of vascular access for haemodialysis (Pisoni *et al.* 2002; Young *et al.* 2002). As such, it is the first option considered for the construction of vascular access for dialysis. The construction of the fistula should be undertaken at least a month prior to the beginning of the dialysis treatment, as specified in the NKF-KDOQIa guidelines (2006). By doing this, a number of potential problems can be prevented, including the urgent need for a catheter and its associated complications, such as infection, bleeding, thrombosis and vessel damage; additionally, the period spent in hospital is reduced. According to Rayner *et al.* (2003), a fistula needs two to six weeks to fully mature. The main objective of health care is to create an AVF for the majority of patients prior to formal haemodialysis for

the first time. Among the advantages of native AVFs are increased blood flow, reduced risk of sepsis, and durability.

2.4.6 Vascular Access

2.4.6.1 Introduction

A suitable type of vascular access has to be created to establish a connection between the circulation system of the patient and the haemodialysis cycle, in order to provide haemodialysis in ESRD patients. There are generally three types of vascular access that can be used for haemodialysis. Of these, the AVF is considered to provide the best long-term functional vascular access, with a reduced risk of thrombosis or infection and is most cost-effective (Manns *et al.* 2005). In addition, AVF does not necessitate multiple interventions and has a lower mortality and morbidity rate among different types of vascular access (Anel *et al*. 2003).

Vascular access problems represent the main determinant of morbidity among haemodialysis patients and put a considerable degree of financial pressure on the healthcare sector (USRDS 2011; UK Renal Registry Report 2011). The three types of constructions of AVFs, which are usually employed, are radiocephalic, brachiocephalic and brachiobasilic (Figure 1). The pre-surgery non-invasive scan imaging help clinicians in the decision making process as to which of these three types would be more suitable for the patient. Often, more than one type could be suitable and the one that is believed to have a higher success rate is chosen. However, when all three options are on the same level, a number of other aspects are included in the decision, such as using the non-dominant arm or a more distally

placed fistula (radiocephalic) to allow in future an easier formation of proximal fistula (brachiocephalic or brachiobasilic) and forming a brachiocephalic fistula over a brachiobasilic fistula due to its ease of formation and less surgical stress.

2.4.6.2 Type of Vascular Access

Successful haemodialysis depends on the provision of safe, efficient, and durable vascular access. Establishing and maintaining effective vascular access is a demanding process for both patients and renal services. These demands are set to increase in response to an RRT population that is becoming increasingly dependent on haemodialysis, whilst also increasing in population size, age, and co-morbidity.

Initially, vascular access methods relied on repeated peripheral cannulation to deliver arterial blood to the dialysis machine and return it to an accompanying vein. In 1949, Alwall, made the first attempt to connect an artery and a vein, using glass cannula and rubber tubing (Alwall et *al*. 1949; Konner 2005). This device would allow blood to be diverted onto an extracorporeal circuit for dialysis when required. His attempt was unsuccessful although it provided the template for the arteriovenous Teflon Shunt developed by Quinton *et al.* (1960). Their device consisted of two Teflon cannula inserted into the wrist, one in the branch of the brachial artery in the forearm and one in the accompanying antecubital vein. The cannula had its external ends connected by flexible tubing from which connection to an extracorporeal circuit could be made. This provided nephrologists with the first permanent vascular access device and was a decisive breakthrough in the provision of haemodialysis to the ERF population. The 'Scribner' shunt, as it came to be known, underwent many refinements before being ultimately superseded by the successful development of

arteriovenous fistulae, arteriovenous grafts, and central venous catheters. Nonetheless, the Scribner shunt played a key role in the development of permanent vascular access devices.

The Arteriovenous Fistula

Cimino and Brescia described a technique where haemodialysis was conducted through a simple puncture of the most accessible forearm vein. Patency of the vein was assured by the use of an inflatable tourniquet. This allowed needles of varying sizes to be used with resultant haemodialysis flows of 150-400 ml/min. Whilst successful, this technique was limited by the poor longevity of peripheral veins in comparison with that of Scribner's external arteriovenous shunt. Logical development of this technique, however, led to the creation of the first internal arteriovenous fistula. The successful use of the new technique was reported in a landmark paper (Brescia *et al*. 1966). The thought process of AVF was based on Cimino treating veterans of the Korean war; some of whom had traumatic AVF due to gunshot wounds and Cimino noted that venesection in these patients was very easy. They reported 12 cases in which successful primary function of an AVF had been achieved by creating a side-to-side connection at the wrist between the cephalic vein and radial artery. Exposure to high-pressure arterial flow was found to promote enlargement and thickening of the venous wall (Figure 4). After approximately six weeks maturation, a robust vessel wall had developed that could sustain repeated cannulation and allow regular haemodialysis to take place.

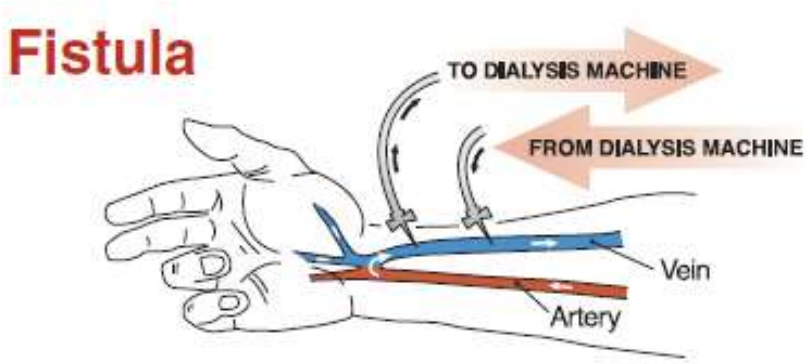


Figure 4. Arteriovenous Fistula (Permission from Arteriovenous Fistula First)

Arteriovenous fistula created by connecting an artery directly to a vein, frequently in the forearm. This artificial connection allows the vein to become larger and for the walls of the vein to thicken, a process termed maturation.

A year later the technique had been amended to allow the construction of an end-to-end anastomosis in the lower arm between the cephalic vein and the radial artery (Sperling *et al.* 1967). This technique restricted arterial inflow into the AVF to that blood delivered by the feeding radial artery led to a high risk of developing steal syndrome (Figure 5).

This is a clinical condition caused by arterial insufficiency distal to haemodialysis AVF due to diversion of blood into AVF. Consequently, the technique latterly became regarded as a secondary option available to surgeons when considering surgical revision of a failed AVF. The technique was further refined in 1968 by Rohl, who devised the radial artery side-to-vein-end anastomosis, with or without the distal ligature of the radial artery to the communicating vessels. This allowed a more suitable positioning of the AVF with excellent subsequent flows. It is the technique that has become the standard AVF creation procedure of choice and has allowed

AVF creation surgery to evolve and successfully provide a range of potential sites for AVF creation, predominately within the upper limbs (Konner 2005).

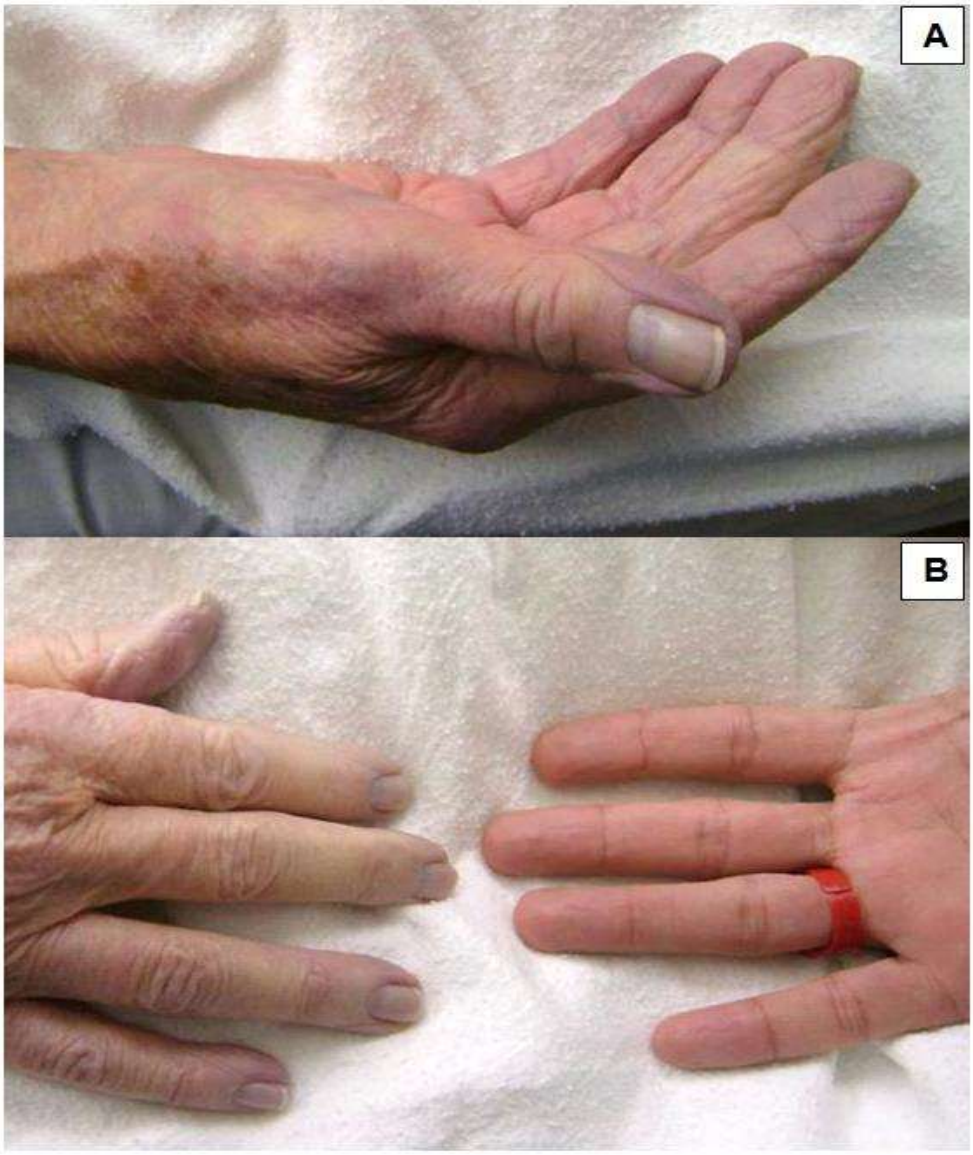


Figure 5. Steal Syndrome after AVF Creation (Adapted from Vachharajani 2010)

After creation of right sided brachiocephalic fistula, patient complained of pain and numbness over right hand. On examination the fingers were blue and cold (A). Panel B compares the colour of her hand to a normal pink colour. Upper arm fistulae are more likely to cause ischemic symptoms compared to forearm fistulae. The presence of poor peripheral vasculature secondary to diabetes, calcification and peripheral arterial disease is the primary etiological factor.

For practical purposes AVF creation is best conducted on the non-dominant arm with use of distal sites where possible; preserving the proximal vascular tree should vascular access surgery be required in the future. The longevity, durability, and favourable complication rate of the AVF have established it as the leading method of establishing permanent haemodialysis vascular access. Around two thirds of haemodialysis patients in the UK dialyse using an AVF (Fluck *et al*. 2007).

Arteriovenous Grafts

An alternative to the AVF is the synthetic arteriovenous graft (AVG). This was devised following the introduction of the Scribner shunt, which was noted to employ a length of flexible tubing to connect the arterial and venous blood flow (Figure 6). Thomas (1969) developed this principle by replacing the cannula with Dacron patches sutured into the vessel wall and bringing out a loop of connecting silastic material to the skin surface. By avoiding the use of intraluminal cannula, this device was less prone to thrombosis (Thomas 1969). Meanwhile, the first vein graft had been performed using a length of excised saphenous vein, to connect the brachial artery to its accompanying vein. By combining each of these three principles direct anastomosis of vessels to tubing, looping a section of tubing to connect artery to vein and subcutaneous tunnelling of the connecting loop, the modern AVG was created (Konner 2005).

Whilst initially Dacron was the most commonly used graft material, the emergence of the synthetic material polytetrafluoroethylene (PTFE) as a pliable, biocompatible material that may be repeatedly cannulated yet maintain its structural integrity, led to significant improvement in the durability of the AVG.

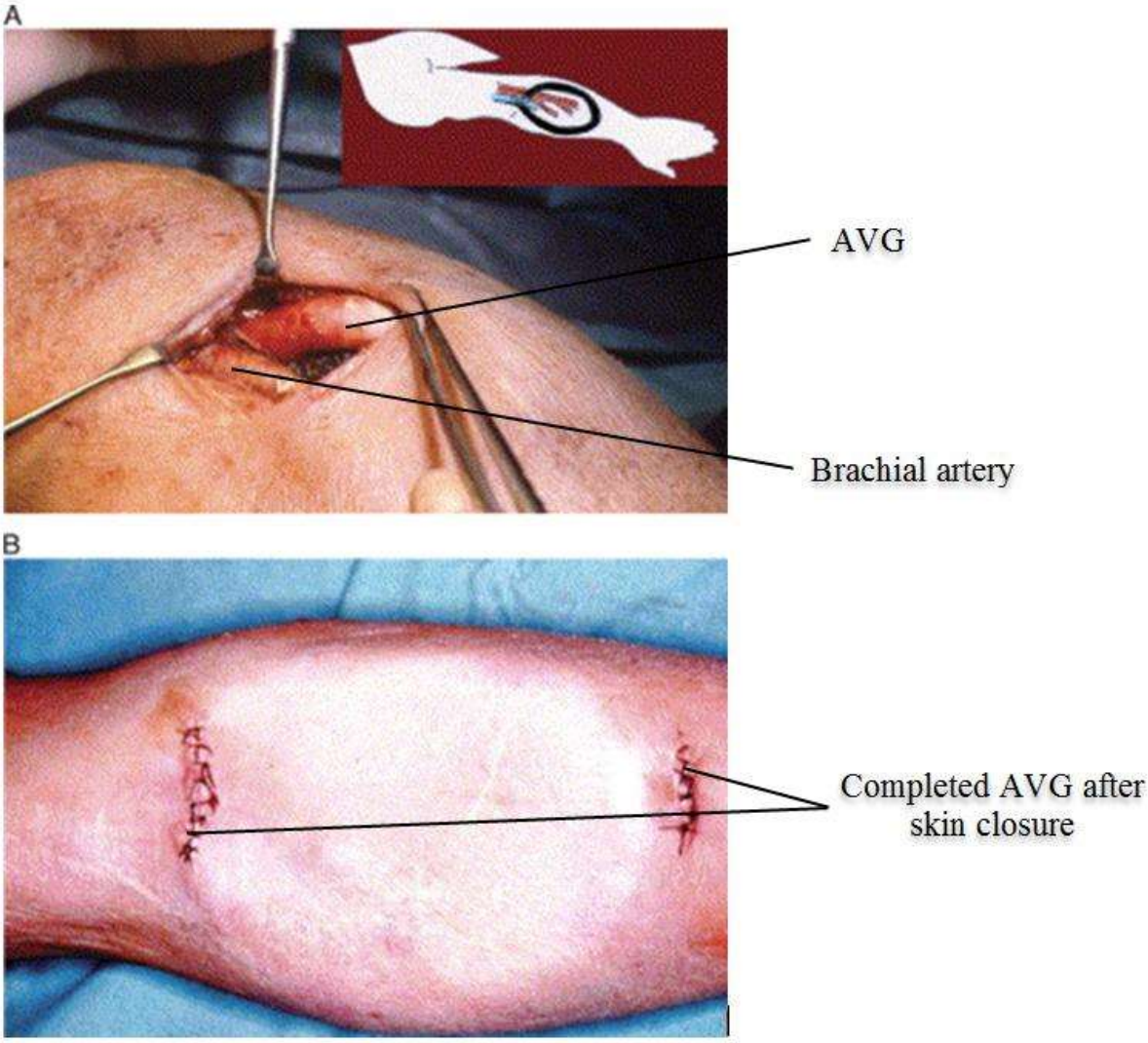


Figure 6. AVG in the forearm (Berardinelli 2006)
A forearm PTFE loop graft: (A) the arterial anastomosis (a) between a tapered e-PTFE and the right brachial artery has been completed. Some oozing of blood through the PTFE can be seen. (B) The completed PTFE loop after skin closure showing the graft in a subcutaneous tunnel in the forearm, with a distal counter-incision.

The brachial artery and the basilic vein are usually connected by way of an AVG. However, it is also common to connect the radial artery and the basilic vein or the brachial artery and the axillary vein with the use of grafts. When vascular access in the upper limbs is exhausted, synthetic grafts can be used to establish vascular access using the subclavian or axillary vessels, femoral vessels, or may even be

anastomosed between the arterial system and the right atrium. Approximately 3% of haemodialysis patients in the UK dialyse via an AVG at present (Fluck *et al*. 2007).

Central Venous Catheters

In the early years of haemodialysis, the demand for experienced surgeons to create arteriovenous shunts, fistula and grafts outstripped supply. The paucity of vascular and transplant surgeons prepared to perform these procedures provoked one UK nephrologist, Stanley Shaldon, to develop hand-made cannulae that could undergo insertion into the femoral artery and accompanying vein to permit immediate haemodialysis access. He made use of the Seldinger insertion technique - a method that enables safe catheter placement into the vascular tree introduced by Sven-Ivar Seldinger in 1953 (Higgs *et al*. 2005; Seldinger 1953).

It was noted that arterial cannulation, in contrast to venous cannulation, is accompanied by an abnormally high risk of bleeding and was soon abandoned. Gradually different insertion sites were used including the jugular and subclavian veins. These had the advantage of allowing central venous pressures to be estimated in patients with extracellular fluid depletion (Shaldon 1994), a common occurrence in many individuals suffering from acute kidney failure requiring dialysis. The insertion of a cannula into the subclavian vein became the favoured approach for CVC insertion until the early 1990s when angiographic data demonstrated a significantly increased risk of central venous stenosis at the site of cannulation. This predisposed patients to a high risk of limb oedema, which could impair the ability to create and maintain a functioning AVF (Schillinger *et al*. 1991).

Insertion into the internal jugular veins (Figure 7) is now regarded as standard practice although femoral venous cannulation is also performed.

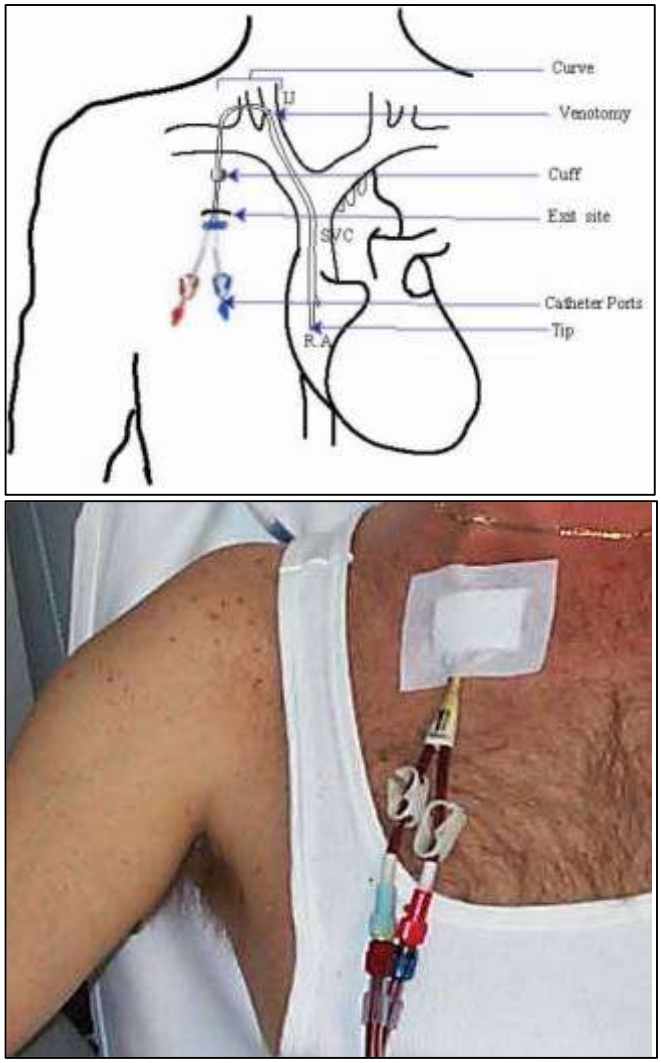


Figure 7. Appropriate tunnel catheter position and anatomy (Banerjee 2009)

The central venous catheter is a flexible synthetic (man-made) tube that is usually placed in a large vein in neck or chest. Dialysis catheters have two lumens attached to two ports (blue and red). The red port draws blood from the body and the blue port returns the blood from the dialysis machine to the patient.

CVCs are frequently used temporarily to provide vascular access for haemodialysis whilst the patient awaits creation or maturation of an AVF or AVG or because they have run out of suitable options for permanent vascular access (Bourquelot 2009).

Some CVCs may be tunnelled subcutaneously en-route to entering the vein with a securing cuff to stabilise the position of the catheter and reduce potential for periluminal infection. Direct transcutaneous cannulation of the vein is often performed acutely and tends not to involve subcutaneous tunnelling or use of a securing cuff. Polyurethane and silicone are the two materials most commonly used in the manufacture of haemodialysis catheters although polymers such as carbothane are increasingly common (Banerjee 2009). These materials provide sufficient flexibility, durability, and biocompatibility for intravascular use.

The catheters are the least preferred modality and, in an ideal setting, no patient should have a catheter as access. Despite the risks associated with dialysis catheters, their use has increased to almost 70% of incident dialysis initiation with catheters (Asif 2008). These different methods of obtaining vascular access allow haemodialysis to be a viable treatment for most of ESRD patients. The diversity of vascular access options available can help nephrologists address a range of clinical scenarios more effectively. Late presentation of ESRD is one frequently experienced scenario that may have a significant impact on vascular access provision. In this setting, the time in which RRT is required to start may arrive before the patient can undergo vascular assessment, surgery, and successful maturation of their fistula. This phenomenon is often used to explain the relatively high prevalence of ESRD patients using CVCs as their first haemodialysis access modality. In the UK renal registry vascular access survey of 2006, 66% of patients started haemodialysis on a CVC compared with 34% using an arteriovenous fistula or an arteriovenous graft. After one year, the percentage of individuals treated with a CVC reached 28% compared with 71% using an AVF or AVG (Fluck *et al.* 2007). UK Renal Association (2011)

suggested that 2/3 of all patients requiring dialysis should start with an autologous fistula and the remaining 1/3 with CVC as these are described as the "Crash Landers" who have acute or undiagnosed renal failure and do not have time for AVF creation and maturation. Similarly, when an AVF or AVG fails, CVCs are a rapid means of establishing vascular access and thus play a significant part in providing urgent vascular access. Whilst each access type has, its relative attributes, it is vitally important to consider the differing degrees of reliability, durability, and complications associated with each approach. Whether considering an individual patient's circumstances or planning vascular access provision at a population level, understanding the range of complications expressed by each access type and which factors predispose to these complications is of fundamental importance in deriving maximum benefit with minimal risk.

2.4.6.3 Functional Outcomes of Vascular Access

As noted by several researchers (Feldman *et al*. 1996; Windus 1993), surgical interventions of vascular access and their associated problems are important causes of morbidity, hospitalisation, and financial pressure. In the US, more than 20% of the total number of haemodialysis patients were admitted to hospital as a result of vascular access and its complications. The costs generated annually amounts to almost $1 billion (Feldman *et al*. 1996). Studies have shown that dialysis grafts made of PTFE are not as long lasting as autologous fistulae (Bender *et al*. 1994; Coburn and Carney 1994); furthermore, they are more likely to develop repeated thrombosis, stenosis, and infection (Churchill *et al.* 1992). The NKF-KDOQIa guidelines (2006) recommend the use of AVFs over AVGs due to the advantages of the fistula; the

AVGs should only be employed when the creation of natural AVFs is due to the exhaustion in the use of the patients veins.

Clearly, there are logistical hurdles to this late presentation to renal services, fitness for surgery, suitable peripheral vascular anatomy, delays due to primary or secondary access failure and slow rates of AVF maturation. Consequently, there remain situations, especially when starting RRT, where use of an AVG or CVC may be required. This is demonstrated by the relative prevalence of CVC use in patients starting RRT around the world. Similarly, CVC insertion is the mainstay of vascular access provision to the acute renal failure population who require haemodialysis. CVCs therefore have an important role in haemodialysis vascular access provision but do so at a cost. USRDS data from 2007 suggest that expenditure on catheter placement is approximately 2.5 to 2.8 times higher than on AVF and AVG surgery. It is suggested that these figures reflect the excess costs the catheter group incur by being a predominately in-patient comorbid population compared to the population who undergo elective AVF and AVG surgery (USRDS 2008). The association between catheter use, comorbidity, and in-patient care is strong. The question of whether the adverse features related to catheter use, such as catheter thrombosis and bacteraemia, are specifically related to use of a catheter or are simply related to the greater level of comorbidity expressed by the population who require catheter insertion has been subject to controversy (Parienti *et al*. 2010).

CVC insertion for haemodialysis is associated with an increased risk for venous thrombosis and subsequent stenosis (Schillinger *et al*. 1991). When manipulated around the obstruction at the innominate vein at the junction of the superior vena

cava, the tip of the catheter or its introducer sheath may wear away the endothelium, prompting to mural thrombosis (Timsit 2003). Catheters are prone to develop infection from 3.8 to5.5 episodes per 1000 days (Hannah *et al*. 2002). Infection can be localized or spread systematically leading to bacteraemia or sepsis (Beathard and Urbanes 2008). In AV graft or within its outflow vein where the graft stitched to the vein, stenotic lesions are found time and again (Bittl 2010). The underlying mechanism is the marked increase in shear stress in the thin-walled outflow vein, which activates focal fibromuscular hyperplasia and initiates a fibrotic venous lesion to develop (Roy-Chaudhury *et al*. 2001; Swedberg *et al*. 1989).

2.4.7 Arteriovenous Fistula and Success

2.4.7.1 Introduction

Vascular access has associated complications that may arise immediately following creation or later during regular use. Failure of vascular access is most frequently due to thrombosis occurring within or around the AVF, AVG or catheter however other significant problems such as infection, aneurysm formation, heart failure, and ischaemia distal to the site of access creation may occur. If the fistula reaches full development it can provide long-term functional access, has a low rate of thrombosis and infection, does not require multiple procedures, and is relatively inexpensive (Asif *et al*. 2006). The prognosis regarding the efficiency of the fistula is made with the help of duplex ultrasound (Costanza *et al.* 2011), which are important instruments that enable the evaluation of the success rate of fistula development and of whether or not it is capable of providing access for haemodialysis (Manns *et al.* 2005; Mendes *et al.* 2002). It may be possible to enhance the results of vascular

access by gaining a more comprehensive picture about the factors involved in the efficient development of fistulae. This can generate important data during the pre-surgery evaluation that surgeons can use to base their decisions on. Thus blood markers if available may be beneficial in anticipating the success of fistula development without the use of invasive tests and is cost-effective.

2.4.7.2 Site and Type of AVF Selection

The growing success rate of treatment of ESRD patients determines durability and the potential for the creation of vascular access. These are usually constructed in the distal location of the non-dominant arm. Patients who do not have vessels in the lower arm adequate for vascular access can have brachiocephalic fistulae. AVF created on the basilic vein of the upper arm, which is of sufficient diameter, is situated at a considerable depth, and thus cannot be opened up during the process of phlebotomy (Allon and Robbin 2002).

Radiocephalic AVF

The standard of vascular access positioning is the radiocephalic direct wrist access, known as the Brescia-Cimino fistula or the ‘wrist fistula’, was first used in 1966 (Brescia *et al.* 1966). As shown in Figure 8, the fistula is constructed by connecting the radial artery to the cephalic vein at the wrist. The procedure usually entails one incision, which enable the surgeon to ligate any venous tributaries that may intervene in the development of the fistula. A number of forms of anastomosis have been used with different outcomes with regard to AVF maturation and steal phenomenon (Rutherford 2000), the cephalic vein end-to-side form being the most frequently

used. It is relatively uncommon to get a steal syndrome with a Cimino fistula (<0.5%), more common in the brachiocephalic fistula (5-12%).

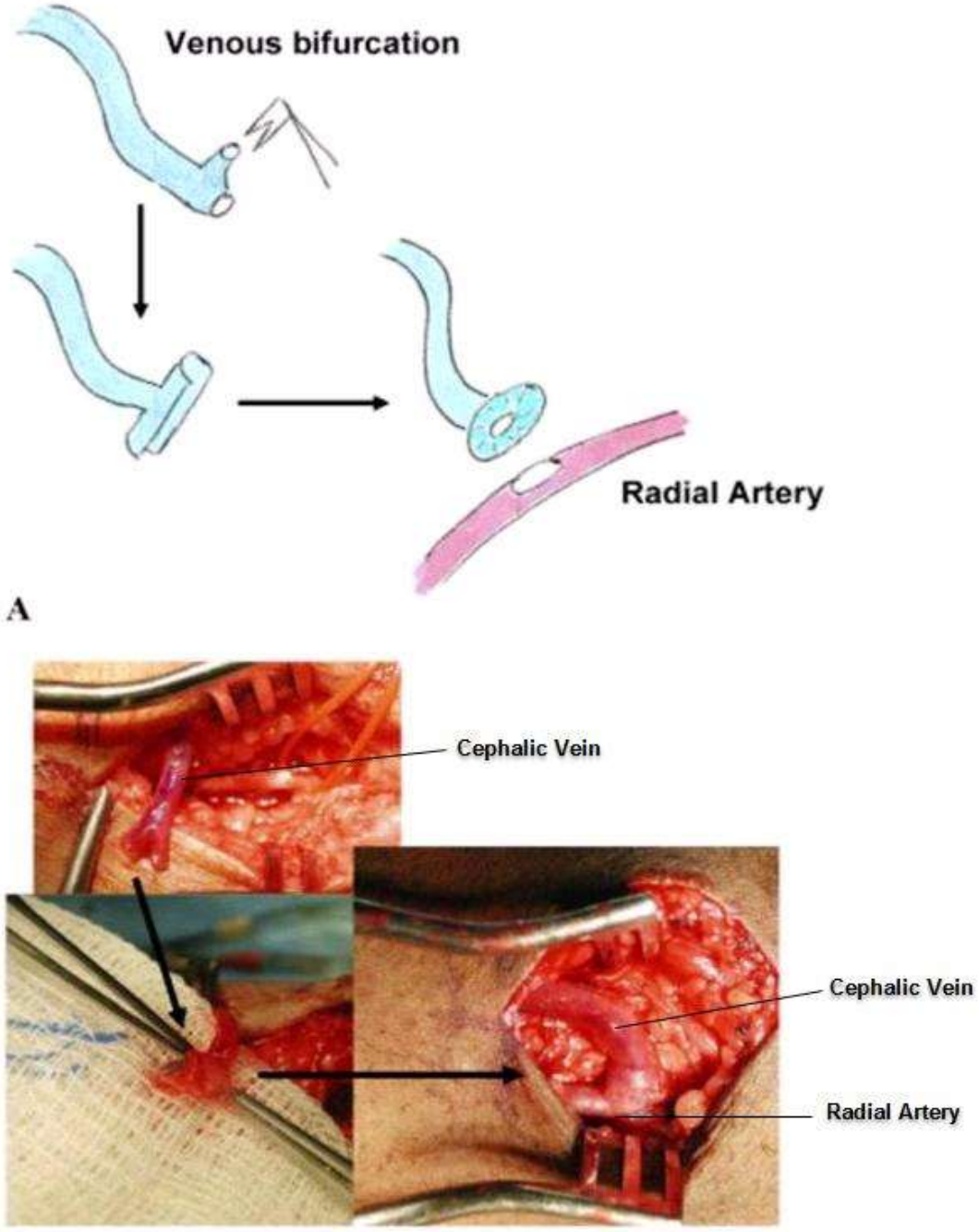


Figure 8. Radiocephalic Arteriovenous Fistula (Allon and Robbin 2002)

Figure shows a radiocephalic fistula which involves end-to-side venoarterial anastomosis of the radial artery and cephalic vein at the wrist. After mobilization and division of cephalic vein branches, the venous bifurcation was opened to create a broad flare or "branch patch". Finally, brad flare was connected with radial artery.

Wong *et al.* (1996) indicated that early failure of the fistula is likely to occur if the diameter of the cephalic vein is below 1.6 mm. The Brescia-Cimino fistula generally has had satisfactory results (NKF-KDOQIb 2006). In the case of autologous access, if the fistula failure or thrombosis does not happen within a year of the procedure then the access rate is bound to be successful.

Brachiocephalic AVF

The process of connecting the cephalic vein with the brachial artery usually has a positive outcome. The autologous access is known as brachial cephalic direct elbow access or brachiocephalic fistula, and is recommended for diabetics as it has a high blood flow and maturation rate (Figure 1). However, it may not be possible to use the rest of the forearm for the construction of additional accesses. Sparks *et al.* (1997) have published the findings of their ten-year study on 111 cephalic vein autologous access. The success rate of brachiocephalic access after 2 years was 66%. Based on these results, the brachiocephalic access was determined to be a beneficial option for patients of advanced age, women, and patients with a history of diabetes. Revanur *et al.* (2000) obtained a maturation rate of 74% after 12 months monitoring of 137 surgical interventions. Another study indicated the higher patency and development rates of primary brachiobasilic and transposed basic autologous accesses, as opposed to brachiocephalic autologous access in 58 diabetics who needed haemodialysis. In this study, 70% brachiocephalic AVF did not mature, in contrast to the much lower failure rate exhibited by primary brachiobasilic access and transposed brachiobasilic fistula, with 27% and 0%, respectively. After a year and a half, brachiocephalic AVFs revealed a collective patency of 33%, whereas the brachiobasilic fistula had a

collective patency of 78% (Hakaim *et al*. 1998). A recent retrospective study conducted by Ayez *et al*. (2012), created 173 autologous upper arm AVFs (87 Bracheocephalic AVF and 86 Bracheobasilic AVF) to compare the maturation, patency, blood flow and complication rates. The study results found no differences between the BC and BB AVF except of surgery time and mid upper arm vein diameters. However, the main weakness of the study was the non-randomised comparison.

Brachiobasilic AVF

The brachiobasilic fistula, or basilic transposition, was first created during the 1970s by Dagher *et al.* (1976) and it generally represents the final autologous access option for the arm (Figure 1). The surgical intervention consists of mobilization, distal sectioning, superficial tunnelling, and the distal end-to-side transfer of the basilic vein to connect with the brachial artery. Several researchers (Davis *et al.* 1986; Zielinski *et al.* 2001) have proposed slightly different interventions, such as lifting the basilic vein instead of transferring it or increase the visibility of the basilic vein in a staged procedure. Overall, basilic transposition has had positive results, particularly in the case of patients who suffer from compromised vasculature distally**.**

2.4.7.3 Complications of AVF

There are a number of problems related to arteriovenous access, including mild symptoms to severe complications. Therefore, it is of the utmost importance to identify and treat such problems to protect patient health, enhance their quality of life, and maintain the AV access in a functional state.

Thrombosis

Thrombosis occurring in AVF is mostly due to intimal hyperplasia secondary to needling AV fistula or mobilization of vein for arterial anastomosis in AVF creation (Beathard *et al*. 2003; Falk *et al.* 2003; Vassalotti 2004). The rate of AVF thrombosis is estimated to be 0.2-0.4 incidents per patient per year, in contrast to 0.8-1.2 incidents per patient per year for AVGs (Woods *et al.* 1997).

The main substrate for venous stenosis is endothelial cell injury, most commonly at the site of the anastomosis. This results in the up regulation of a pro inflammatory cascade, which promotes smooth muscle cell accumulation at the site of injury (Stracke *et al*. 2002). This process may be accelerated in response to shear stress arising from turbulent flow (Sterpetti *et al*. 1992), repeated cannulation and the relative difference in vascular elasticity either side of the anastomosis (Hofstra *et al.* 1994). Other contributing factors include compression of the fistula or graft between dialysis sessions, hypotension, hypovolaemia, and hypercoagulable states (Windus 1993).

Primary prevention of AVF stenosis has focussed on selecting an appropriate site for vascular access creation, as determined by vascular imaging, and monitoring fistula performance. Monitoring relies on assessment of access structure, assessment of access blood flow, measurement of delivered dialysis dose and assessment of the resistance to blood flow on return to the venous tree. These features may all contribute towards determining whether an AVF is at risk of failure. Where narrowing of veins more than 50% is discovered, percutaneous angioplasty or surgical revision may improve AVF longevity. Intervention on a thrombosed AVF is

not likely to lead to restoration of long-term patency, but if an acute, unexpected deterioration in AVF performance occurs, then patency should be restored without delay. Monitoring of AVF occurs routinely as part of a regulated screening programme and undertaken in response to clinical deterioration in a previously functioning AVF. Best practice remains uncertain. Despite the fact that many of the methods used in detecting venous stenosis and thrombosis are effective, routine screening with subsequent intervention has not been proven to reproducibly increase the long-term survival of AVFs. Along these lines, prospective monitoring remains debatable (Sands 2005).

Some guideline groups are recommending some form of prospective monitoring for all AVFs and AVGs (K/DOQI 2006) whilst others recommend restricting detailed AVF and AVG assessment to those with clinical signs of deterioration such as a decrease in intra dialytic blood flows (UK Renal Association 2007).

The issue of antiplatelet agent use in preventing AVF or AVG thrombosis is unresolved. Several antiplatelet agents including aspirin, dipyridamole, clopidogrel, sulfinpyrazone and ticlopidine have been studied in the past. Many of the studies were conducted in the 1970s and 1980s where dialysis populations and treatments were very different to those seen today (Antiplatelet Trialists' Collaboration 1994).

A randomised controlled trial evaluated use of aspirin and clopidogrel although the study was stopped early because of a significantly elevated risk of bleeding among those receiving antiplatelet therapy (Kaufman *et al*. 2003). More recently, the effects of dipyridamole, 200 mg being administered twice every day, plus aspirin, 25 mg administered twice every day, or placebo were evaluated using a randomised

controlled trial of 649 patients with a new AVG. The intervention group demonstrated greater rates of primary patency with a similar rate of adverse events, including bleeding, albeit in a population designed to be of low bleeding risk and with relatively short exposure to the antiplatelet on trial (Dixon *et al*. 2009). Use of anticoagulants such as warfarin has not been proven to reduce thrombosis and the likelihood of it being accompanied by abnormal bleeding is high (Crowther *et al.* 2002).

Infection

Infection is a frequent challenge among the haemodialysis population and accounts for growing rates of hospitalisation, comorbidity, and mortality. USRDS (2008) report demonstrates recent trends in admissions for principle diagnoses of infection and bacteraemia/septicaemia in the ESRD population. It has been found that approximately 20% of vascular access loss is due to the development of infection.

Vascular access is the source of the majority of infections within haemodialysis units. The predominance of skin commensals as pathogenic organisms in bacteraemic patients suggests that inoculation during vascular cannulation is the main mechanism by which infection arises (Higgins 1989). Once inoculated, synthetic materials such as those used in AVGs have a tendency towards chronic infection due to their lack of innate immune defence mechanisms and their propensity to develop a bio film compared with autologous AVFs.

Prevention and treatment of AVF infection is a major element in the safe provision of haemodialysis. When considering arteriovenous fistulae and grafts, sterile

cannulation is fundamentally important. Poor cannulation technique, often due to relative inexperience of the dialysis practitioners, may lead to pseudo aneurysm formation or the development of peri fistula haematomas, which is associated with subsequent infection, and failure of the fistula (Fan and Schwab 1992).

Routine antibiotic prophylaxis is controversial. Topical antibiotic use has not been found to be effective with benefits in reducing nasal *Staphylococcus aureus* carriage by topical mupirocin treatment being found to be associated with the development of resistant pathogens (Laupland and Conly 2003). Consequently most primary prevention strategies focus on the ability to ensure aseptic technique when inserting or handling vascular access devices.

Steal Syndrome

Early thrombosis, infection, and distal ischaemia are the most frequently seen problems related to dialysis access surgery. Stolic (2013) notes that diabetics and the elderly face a high risk of ischaemia and steal syndrome. Suding and Wilson (2007) illustrate the range of ischaemic issues linked to upper extremity dialysis access including amputation of hands or fingers due to ulceration, tissue necrosis or distal gangrene or nonthreatening complications including discomfort, loss of strength, tingling and paleness in fingers which all pass. Schanzer *et al.* (2006) show that blood flow of the hand is not compromised by AVF in the majority of instances although Goff *et al.* (2000) and Leon and Asif (2007) have shown that 1.6 to 8% of people do develop unilateral ischaemia in their hand. Overall, ischaemia in the hand with a fistula requires particular circumstances, first and foremost low perfusion through the arterial system because of arterial occlusive disease proximal or distal

from arteriovenous anastomosis. When overly high levels of blood flow occur through a widened blood vessel with lowered collateral perfusion and inadequate vascular modification, steal syndrome becomes a possibility. Schanzer *et al.* (2006) note that while extreme and prolonged hypoperfusion can result in the death of tissue and compelling amputation of the fingers or forearm, this occurs in only 1% of patients and ischaemia is usually minor.

AVF Maturation

As indicated by Allon and Robbin (2002), the growth of fistula prevalence is hampered by early AVF failure caused by thrombosis or lack of development. An arteriovenous fistula is considered as "failure to mature" if it does not develop sufficiently enough to withstand dialysis or if it blocks during the first three months following construction (Beathard *et al.* 2003). Fistula development depends mainly on two factors; appropriate blood flow to maintain the dialysis circuit and adequate vessel diameter to enable repeated insertions of cannulae. As such, it is very important to intervene accordingly to maintain fistula patency. Most AVFs, which fail early on, have exhibited injuries caused by thrombosis or stenosis inside the access circuit (Beathard *et al.* 2003). It has to be kept in mind that stenosis occurs gradually which in the end results in total vessel occlusion, thus degenerating into access thrombosis (Asif *et al*. 2006).

A clinically immature fistula is defined as a fistula having one or more of the following characteristics, as determined at physical examination by the dialysis nurse or surgeon: *(a)* appear to be inadequate at inspection (discolouration/swelling), on palpation and auscultation (absence of thrill) *(b)* small-calibre vein at palpation, such

that it would be difficult to cannulate the vein with a 17-gauge dialysis needle; *(c)* less than 10 cm of palpable or visible draining vein length to allow cannulation (Allon and Robbin 2002; Robbin *et al*. 2002).

2.4.8 Prediction of Maturation of AV F

2.4.8.1 Introduction

The care of patients suffering from CKD, prior to and during the dialysis treatment, is largely inefficient and uncoordinated, which has a negative influence not only on patient recovery but also on the healthcare sector (Rastogi *et al.* 2008). The proper functioning of the AVF is vital for the haemodialysis treatment and, as such, it is the main concern of kidney specialists and vascular surgeons. In the case of ESRD patients, the autologous fistula is the most suitable vascular access option. It has the lowest mortality rate in comparison to AVG and CVC, and has the lowest rate of re-intervention (Konner *et al*. 2003). Due to these advantages, the NFK-DOQI guidelines endorse the use of native AVF, which has been noted to have a 65% primary success rate amongst patients about to commence haemodialysis (Brouwer *et al.* 2006). Konner *et al*. (2003) had also obtained a high success rate (70-90%) of native AVF construction in their study on a randomised sample of ESRD patients. Despite the fact that it is not without its faults, the arteriovenous fistula offers better quality access for dialysis as it has a long-lasting primary patency rate, does not necessitate numerous procedures, and has the most reduced rates of morbidity and mortality among all types of vascular access (Anel *et al*. 2003).

Being able to generate a prognosis regarding the cases in which the arteriovenous fistula is more likely to reach maturity, without additional procedures, would contribute to an increase in the prevalence of AVF construction and use. In cases where the chances of the fistula maturation are very low, an arteriovenous graft can be used. The previous studies on the assessment of predictive markers of fistula maturation varied to a great extent with regard to definitions, design, size of the study, patient sample and clinical aspects (Wang *et al*. 2011; Monroy-Cuadros *et al*. 2010; Lok *et al.* 2005; Feldman *et al.* 2003; Huber *et al.* 2002; Robbin *et al.* 2002). As a result, surgeons and specialists are faced with the task of deciding which possible risk factors are more likely to occur than others, as well as which parameters to employ when evaluating the success rate of fistula development in patients awaiting the creation of a permanent access.

The prognosis regarding the efficiency of the fistula is made with the help of duplex ultrasound, which are important instruments that enable the evaluation of the success rate of fistula development (Manns *et al.* 2005; Mendes *et al.* 2002). It may be possible to enhance the results of vascular access by gaining a more comprehensive picture about the factors involved in the efficient development of fistulae. In addition, this can generate important data during the pre-surgery evaluation that surgeons can use to base their decisions on. Independent predictive markers may be beneficial in anticipating the success rate of fistula development without the use of invasive tests and using tests that are cost-effective. The aim of the study is to formulate a simple, economical, clinically feasible, and easy to use prognostic model to provide an accurate prediction regarding the rate of successful development of each AVF.

2.4.8.2 Endothelial Function and AVF Maturation

a) Role of Endothelium

The endothelium is the largest organ in the body consisting of endothelial cells (ECs) lining every blood vessel. Augustin *et al*. (1994) reported that adults possess enough ECs that cover a surface area of approximately 1 to 7 m^2, with a total weight of around 1kg, and a total quantity of 1,013-6,078 individual cells. In healthy subjects, vascular endothelium has many functions: it is able to identify hormonal stimuli (vasoactive substances) and mechanical stimuli (pressure and shear stress). ECs are able to regulate inflammation, cell proliferation, coagulation, and vascular tone due to their output of a number of compounded substances (Kolluru *et al*. 2012). Endothelium produced vasodilatory materials such as C-type natriuretic peptide, various endothelium-derived hyperpolarising elements, prostacyclin, and nitric oxide (NO), whereas vasoconstrictor materials are reactive oxygen species, thromboxane A2, angiotensin II, and endothelin-1 (Schiffrin 2001). In addition, there are a number of inflammatory regulators, such as nuclear factor-kB (NF-kB), vascular cell adhesion molecule-1, E-selectin, NO, and intercellular adhesion molecule-1. Gresele *et al*. (2010) reported that fibrinogen, prostacyclin, thromboxane A2, plasminogen-activator inhibitor-1, NO, tissue factor inhibitor, von Willebrand factor, and plasminogen activator act as modulators for haemostasis. Permeability, inflammation, coagulation, cell adhesiveness, and vascular tone are among the variety of local blood vessel operations modulated by endothelium. Antonov *et al*. (1997) stated that in medium to large arteries, healthy ECs contribute to the prevent atherosclerosis by inhibiting platelet activation, limiting the entry of cells and lipids

into the vessel wall, maintaining a non-proliferative and biochemically inactive intima.

b) Endothelial Dysfunction

Deanfield *et al*. (2005) explained that endothelial dysfunction occurs when there is an imbalance between the, vasoconstricting and vasodilating materials (produced directly or indirectly by the endothelium). Goligorsky (2005) stated that endothelial cell dysfunction can be caused by multiple factors such as genetics, advance glycation end products, hyperglycaemia, high blood cholesterol, hypertension, obesity, diabetes, and smoking. Endothelial dysfunction is associated with higher aggregation of platelets, anticoagulant properties, decreased production of NO and higher secretion of cytokines, chemokines, or adhesion molecules and increased reactive oxygen species production from the endothelium (Al-Isa *et al*. 2010). Furthermore, Dandona *et al*. (2004) and Yu and Lyons (2005) found that individuals suffering from chronic kidney failure exhibit EC dysfunction. There is also a link between metabolic changes to nitric oxide synthase (NOS) and chronic kidney disease. Kharbanda and Deanfield (2001) explained that NOS is available to ECs in two types of isoforms; inducible and constitutive or iNOS and cNOS, respectively. Physiological vascular dilation is significantly affected by the constitutive isoform. In patients with advanced renal disease, NO production decreased from cNOS has been observed as a mechanism leading to impaired endothelium-dependent vasodilation in uraemia (Santoro *et al.* 2010). Furthermore, Passauer *et al*.'s (2005) research found a correlation between reduced NO production and reduced endothelium dependent vasodilation in dialysis patients.

Endothelial dysfunction has been conclusively shown to b e an early event in the progression of atherothrombosis and to have a predictive value for future ischaemic cardiovascular events (Deanfield *et al*. 2007; Verma and Anderson 2002). In the context of arterial ischaemic cardiovascular disease, endothelial dysfunction and in particular a reduction of the biosynthesis or of the biologic activity of NO, has been identified as a fundamental component of the pathophysiology of atherosclerosis and shown to be associated with risk factors such as hypercholesterolaemia, hyperhomocysteinaemia, diabetes, hypertension and smoking (Deanfield *et al*. 2007). Endothelial dysfunction is coupled with an increased oxidative stress and inflammatory changes that play a role in the development and progression of atherosclerosis in the early stages, while they increase the vulnerability of fully developed plaques facilitating their rupture (Verma and Anderson 2002).

c) Endothelium and its effect on AVF Maturation

Early fistula failure is usually due to thrombosis which can be triggered by haematoma, low flow rates resulting from low blood pressure, or by a hypercoagulable state (Konner 2000). On the other hand, research by De March *et al*. (1996) and Mysliwiec (1997) showed that progressive neointimal hyperplasia in the venous outflow system can lead to stenosis, which can cause late thrombosis of haemodialysis AVF. Arteriovenous fistula anastomoses need swift proliferation of endothelial cells to restore the barrier, permeability, biochemical monitoring roles of ECs in managing vascular repair, local thrombosis, neointimal hyperplasia and inflammation (Cowan and Langille 1996). Because the migration and proliferation of ECs are restricted by uraemia, and because uraemia causes abnormal vascular

remodelling, neointimal hyperplasia can sometime be found at the point of anastomosis of vascular access. This results in primary access failure and ineffective dialysis (Roy-Chaudhury *et al*. 2006).

Erdem *et al*. (1996) discovered that during haemodialysis, turbulent flow, intraluminal pressure and regular needle insertion caused endothelial damage, which led to haemostatic activation in AVF. Wakefield *et al*.'s (2008) study indicated that thrombus development and blood clotting could be stimulated by higher levels of factor V, plasminogen activator inhibitor-1, tissue factor and von Willebrand factor, as secreted by a dysfunctional venous endothelium. Furthermore, a dysfunctional venous endothelium favours the interactions with circulating tissue factor-bearing micro particles, further triggering localised blood clotting activation (Del Conde and Lopez 2005).

According to Rekhter *et al*. (1993) and Kim *et al*. (2006), vascular stenosis of arteriovenous fistula is primarily the result of neointimal hyperplasia. The pathophysiology of neointimal hyperplasia consists of occurrence of extracellular matrix deposition, and proliferation, adherence, and migration of vascular smooth muscle cell (VSMC), which represents abnormal healing of wounds. Sung *et al*. (2008) found that growth factors and cytokines act as semi-regulators for the changes to the VSMC response. Tumor necrosis factor-α (TNF-α) stimulates the synthesis of other pro-inflammatory cytokines and adhesion molecules; it has a chemotactic activity for monocytes and stimulates migration and proliferation of VSMC. Additionally, inflammation is reduced by interleukin-10 due to its ability to hinder

cytokines such as TNF-α, which cause inflammation, and it also ceases the activation of inflammatory cells (Sung *et al.* 2008).

Atherosclerosis and intimal thickening occuring at the bifurcation point of carotid artery in the area of low wall shear stress without unidirectional flow and with flow separation (Zarins *et al*. 1983). The association between intimal thickening, low wall shear stress, and low blood flow has also been demonstrated by several studies in different vascular models (Glagov *et al*. 1988; Mattsson *et al*. 1997; Guzman *et al*. 1997). Paszkowiak and Dardik (2003) explain that shear stress represents the force of blood's friction against the wall of the blood vessel. The researchers have shown that an increase in shear stress usually results in endothelial rest and survival. In addition, higher levels of shear stress can also lead to the expression of regulators that prevent coagulation and inflammation, and can cause the endothelial cells to move along with the blood flow (Chiu and Chien 2011). As Guzman *et al*. (1997) and Keren (1997) explained, this generally leads to a lower level of neointimal hyperplasia and vessel dilation.

The shear stress levels revert back to baseline due to these vascular reactions. On the other hand, the activation of ECs and proliferation, release of inflammatory and procoagulant substances and alterations to cellular shape, are all events that have been linked to reduction in shear stress and blood flow. This manifests as raised levels of neointimal hyperplasia and vascular constriction (Meyerson *et al.* 2001; Honda *et al*. 2001). Furthermore, Dardik *et al*. (2005) has revealed that vascular response seems to be significantly influenced by the exact type of shear stress. For instance, matrix metalloproteinase up-regulation, higher proliferation of cells, and a

pro-inflammatory environment can be caused by oscillatory shear stress (Gambillara *et al*. 2005). On the other hand, normal dilatation and endothelial stability are the outcomes of laminar shear stress (Honda *et al*. 2001).

Corpataux *et al*. (2002) discovered that the fistula vein instantly deal with huge increase in blood flow following the creation of AVF. Additionally, there is an eventual thickening of the fistula vein wall and dilation of the venous lumen. This allows the fistula vein to be effectively deliver sufficient blood for haemodialysis and can be regularly needled for dialysis circulation. The next most significant hemodynamic factor that typically influence on an AV fistula is the circumferential or transmural pressure. Transmural pressure is produced inside the blood vessel, previous studies (Lehoux *et al*. 2006; Lehoux *et al*. 2004; Hayashi *et al*. 2003) have shown that increase in transmural pressure lead to an activation of smooth muscle cells, higher levels of extracellular matrix elements, and raised production of cytokine. These pathways invariably leads to the thickening of blood vessel wall, which resulted in a reduction of transmural pressure revert back to basal level.

The influence of hemodynamic factors on the remodelling of freshly-generated arteriovenous fistula has been investigated by Corpataux *et al*. (2002), who employed Doppler ultrasound methods and echo-tracking to assess blood flow and pressure, vessel diameter, and the thickness of cross-sectional walls immediately after patients had been operated on. The researchers investigated the same variables at the 1 and 3 month post-surgery stages. The researchers found that blood flow rose to 539 ml/min (range 325-990 ml/min) during the initial post-surgery week. This caused the mean shear stress to rise from its standard level of 5-10 dyne/cm^2 to 24.5 dyne/cm^2.

Additionally, the cephalic vein's internal diameter rose from 2,370-4,430 µm at week 1 (before the operation), to 5,041 µm at the 1 month mark, and to 6,620 µm at the 3 month mark. This pattern was caused by a reduction in shear stress, which dropped to a standard value: 18.1 dyne/cm^2 at the 1 month, and 10.4 dyne/cm^2 at the 3 month. Therefore, a negative correlation was found between vessel diameter and shear stress. Additionally, the cephalic vein's cross-sectional wall gradually increased, measuring 4.4 mm^2 at the 1 week, 5.3 mm^2 at 1 month, and 6.9 mm^2 at 3 months, with a p value of < 0.028. This suggests that the vascular mass had risen. This being said, luminal stenosis did not occur due to the rise in the cross-sectional wall area. This was due to the rise in the diameter of the cephalic vein. Throughout the study, there were no fluctuations in the AV fistulae's blood pressure.

Vahholder *et al*. (2001) and Cardinal *et al*. (2007) indicated that wound healing, migration, proliferation, viability, and other fundamental EC biological processes are restricted by the uraemic toxins found in the plasma of individuals with ESRD. This is particularly true at the site of haemodialysis vascular access. The failure of these EC processes has played crucial role in vascular remodelling. According to Chitalia *et al*. (2011), vascular remodelling is negatively impacted by EC dysfunction that is caused by uraemia. The result of this is vascular access failure, can be fatal to patients with ESRD since it is crucial to achieve vascular access for haemodialysis.

2.4.8.3 Blood Markers and Factors in the Maturation of AVF

According to Irish *et al.* (2009), vessel obstruction or immaturity account for 20-54% of cases of primary failure of arteriovenous fistula. The maturity of fistula is believed to be reduced by a number of demographic and clinical elements. Pisoni *et al.* (2002)

and Allon *et al.* (2000) indicated that a high rate of AVF maturation is influenced by a lower BMI, young age, male gender, and the absence of PVD and diabetes.

a) Age as a factor for AVF Maturation

It is possible that older people are at greater risk of diabetes and peripheral vascular disease. A meta-analysis of 13 cohort studies (of which 11 were retrospective) provides the best available evidence and finds that elderly individuals with radiocephalic AVFs had a higher primary failure rate and decreased patency (Lazarides *et al*. 2007). However, the definitions of "elderly" in the included studies ranged from 50 to 70 years, and the review was specific to wrist AVFs.

Comparative studies on AVF patency in elderly and younger individuals has been conducted by Ridao-Cano *et al.* (2002), Obialo *et al.* (2003), Lok *et al.* (2005), Kim *et al.* (2006), Jennings *et al.* (2009) and Swindlehurst *et al.* (2011). In particular, the effect of the intima-media width of radial arteries on early failure of radiocephalic AVF was studied using ninety individuals with ESRD who had undergone vascular access surgery (Kim *et al.* 2006). The surgery removed 10mm long partial arterial walls using an elliptical type of microscopic analysis and a link between higher age and higher AVF maturation failure and intima-media width was revealed. The result of higher intima-media width is the loss of vascular elasticity and the vessel luminal narrowing causing a rise in arterial rigidity. Yan *et al.* (2010) showed that a separate risk factor for intima-media width in kidney disease patients is diabetes.

Other studies, however, did not support worse AV fistula patency rates in patients. Lok *et al.* (2005) conducted a single-centre, retrospective analysis of over 440 AVFs.

The study compared the results of AVF in different age groups finding that the construction of AVFs should not be affected by age. However, single centre study results may limit its external generalizability. Other studies results also showed no relationship between primary AVF patency rates and age. Thus, the link between degree of AVF success and age is unclear and no definite conclusions can be made (Swindlehurst *et al.* 2011; Weale *et al.* 2008; Burt *et al.* 2001; Wolowczyk *et al.* 2000).

b) Gender as a Factor for AVF Maturation

Research is now questioning the traditional belief that men have larger vessel diameters than women. In the Haemodialysis (HEMO) Study, female gender was identified as a significant predictor of AVG rather than AVF use (Allon *et al*. 2000), but there is little specific evidence for AVF patency differences between genders. A longitudinal study (Astor *et al.* 2000) examined vascular access complications in a large cohort (n = 833) of haemodialysis patients who had a permanent access in use one month after starting haemodialysis therapy and compared complications in men and women. The study found that female gender was associated to a relative hazard of 1.58 (95% CI, 1.05 to 2.35) in AVF patients as compared to male gender. However, a retrospective study of over 190 individuals did reveal variations in vasculature between men and women. Vessel diameters were calculated at twelve arterial sites and seventeen venous sites revealing that no considerable variations exist in these diameters between genders. Furthermore, meta-analysis by Rooijens *et al*. (2004) indicated that men and women's one-year patency levels and maturation for radiocephalic AVFs is similar.

c) Coagulation Factors (PT, INR) as a marker for AVF Maturation

Arteriovenous fistula dysfunction remains a major contributor to the morbidity and mortality of patients on haemodialysis (Vachharajani 2012). The failure of a newly created AVF to mature and development of stenosis in an established AVF are two common clinical predicaments. The commonest cause of failure of a mature AVF is stenosis of the venous segment, with 20–40% occurring within the first few centimetres of vein distal (upstream) to the anastomosis known as the "swing segment" (Conte *et al*. 2009).

Chang *et al.* (2005) observed that the infiltration of a great number of macrophages and a various number of lymphocytes in the vascular lining of an obstructed AVF caused a considerable increase in inflammatory activity. It has long been recognised that the endothelium plays a vital role in the prevention of thrombosis, regulation of coagulation and lipid transport (Tooke and Lowe 1996). Atherosclerosis can lead to disruptions to the vascular endothelium, which enables platelets to accumulate and fasten to the endothelium, and initiate the clotting outpouring. This could potentially degenerate into obstruction of the vessel (Pearson 1994). When the endothelium deteriorates, the endothelial cells produce and release in the plasma a variety of substances such as plasminogen-activator inhibitor-1, von Willebrand factor, thromboxane A2, fibrinogen, tissue factor, which can be used as indicators of the degree of endothelial disruption (Galley and Webster 2004; Verma and Anderson 2002).

Warfarin prevents coagulation within the AVF, potentially prolonging the duration of patency. A double blind randomised controlled trial (Crowther *et al.* 2002) was

performed to compare the response triggered by administration of low intensity warfarin (variation in dosage but intended to maintain an international normalised ratio of 1.4 to 1.9) to the response triggered by placebo in maintaining the patency of prosthetic AVGs. A random sample consisting of 107 participants, 56 being administered warfarin and 51 being administered placebo, was used and monitored for two years. The warfarin group revealed an overall graft loss of 73%, whereas the placebo group exhibited a 61% loss. Major bleeding was experienced by those treated with warfarin (six cases versus zero). The study was stopped prematurely due to serious side effects. Therefore, the risk-benefit does not favour anticoagulation unless there is another established indication.

Grontoft *et al.* (1998) double blind randomised controlled study aimed to verify that ticlopidine is both a successful and harmless way of decreasing AVF early failure rates. The study consisted of 258 individuals from nine dialysis centres in Linkoping, Sweden, who were offered AVF construction for haemodialysis. For a week prior to the procedure and for four weeks following it, the medication (either a placebo or ticlopidine) was administered to the study participants. The findings revealed that 19% of the study subjects given the placebo developed thrombosis whereas only 12% of the study subjects who were given ticlopidine developed thrombosis. In regards to preventing thrombosis following AVF procedures, however, the results did not reveal that ticlopidine had any noteworthy effect.

Dember *et al.* (2008) carried out a randomised, double blind, and placebo-controlled trial in numerous centres in United States, which focused on the effects of clopidogrel administration to a sample of 877 patients suffering from advanced CKD

or ESRD, who had just undergone surgery for fistula construction. However, the statistical power of the study to detect the effect of clopidogrel on the outcome was limited because the achieved sample size of 877 was 32% smaller than the target sample size. The goal of this study was to evaluate the impact of platelet suppression on AVF thrombosis and maturity of AVF. Fifty-three patients (12.2%) who had been administered clopidogrel developed fistula thrombosis, in contrast to 84 patients (19.5%) who had been administered placebo. The study results concluded that clopidogrel reduces the incidence of early thrombosis of new arteriovenous fistulas.

A systematic review was conducted by Osborn *et al.* (2008) to identify the influence of adjuvant drug therapy on fistula and graft patency rates in patients diagnosed with ESRD. A total of ten randomised controlled trials using anti-platelet drugs such as ticlodipine, aspirin, dipyridimole and clopidogrel or anti-thrombotic drug treatment to prevent blockages in the artery and vein access points for dialysis was included. Results showed that antiplatelet drugs, including ticlopidine, aspirin, and clopidogrel, had a positive influence. As such, it would seem that the administration of antiplatelet drugs to patients with AVF is feasible. However, most of the included trials had a short follow-up period so that any benefits in the longer term are not clear.

d) Lipid Profile (TC, TG, HDL) as a marker for AVF Maturation

Thrombosis of AVF is an important cause of morbidity among patients undergoing haemodialysis. The part that serum lipid profile plays in this is still largely unknown. Kirkpantur *et al.* (2008) conducted a retrospective three-year study on a group of 99 patients to analyse the connection between serum lipid profile and fistula thrombosis.

The study results showed that the serum levels of cholesterol and the levels of triglyceride observed in patients with fistula thrombosis and those with functional fistula were similar. Nonetheless, the former exhibited considerably reduced high-density lipoprotein and albumin, higher low-density lipoprotein and serum C-reactive protein levels than the latter.

The features of classic uraemic dyslipidaemia are high levels of triglyceride, reduced high-density lipoprotein, and overall concentration of cholesterol. Advanced kidney failure enhances these features, whereas RRT and co-morbidity, such as diabetes mellitus, alter the features (Chan *et al.* 2008). In association with CKD, atherosclerosis progresses more rapidly and it manifests as extremely calcified plaques which adhere to the subintimal layers of the artery wall. One of the reasons for this is that lipids in high concentration interfere with the mediators (angiotensin II, endothelin-1, plasminogen activator inhibitor-1, Prostacylin, and Nitric oxide) believed to impact on renal function (Heymann *et al.* 2012). A long-term case-control study in 60 patients with autologous AVF was carried out to analyse the effect of drugs or factors on AVF patency. Mean follow up time was 25 months. Study results showed improved fistula patency (71.5 *versus* 39.1%) at 2 years in patients taking folic acid and statin compared to those on no statin therapy (Righetti *et al*. 2009). However, in this small, single centre study, no significant difference was noted in HDL, LDL, TG and TC except homocysteine ($p<0.01$).

e) Urea, Creatinine and Electrolytes as a marker for AVF Maturation

The pre-operative treatment of individuals suffering from CKD or dialysis-based ESRD is made difficult by the actual renal condition, with the accompanying

disruptions of fluid and electrolyte homeostasis and damaged drug filtration system, as well as by co-morbidity, such as diabetes mellitus, chronic hypertension, cardiovascular and cerebrovascular disease. Several studies (Roy-Chaudhury *et al.* 2007; Schwab *et al.* 1997; Windus 1993; Fan and Schwab 1992) have revealed that, in up to 80% of cases, vascular access breakdown is brought about by vascular obstruction in conjunction with pre-existing stenosis of the draining vein of the AVF.

In arteriovenous fistula, thrombosis can also be caused by inflammation. In their study, Churchill *et al.* (1992) found that AVG obstruction was most frequently determined by hypoalbuminaemia. Further studies have revealed that hypoalbuminaemia, apart from being a sign of dietary deficiency in uraemic patients, is also a symptom of inflammation (Kaysen and Don 2003; Kaysen *et al.* 2000; Stenvinkel *et al.* 1999). From these, an indirect conclusion may be drawn that inflammation is involved in AVF thrombosis.

Endothelial cell dysfunction is often observed in individuals with impaired kidney function (Yu and Lyons 2005; Annuk *et al*. 2001). Plasma from patients with ESRD or uraemic toxins, inhibit fundamental endothelial cell biological processes such as viability, proliferation, migration and wound healing (Cardinal *et al*. 2007; Vanholder *et al*. 2001). Abnormalities in these endothelial cell functions play a key role in vascular remodelling, especially at the site of dialysis vascular access. Arteriovenous fistula require rapid proliferation of endothelial cells to restore the barrier, permeability, biochemical regulatory functions of endothelial cells in controlling vascular repair, local thrombosis, inflammation and neointimal hyperplasia (Cowan and Langille 1996). Since uraemia inhibits endothelial cell

proliferation and migration, and eventually results in abnormal vascular remodelling, neointimal hyperplasia at the site of anastomosis of vascular access is common. This results in primary access failure and ineffective dialysis (Roy-Chaudhury *et al*. 2006).

The association between endothelial function and early stage progressive kidney disease has been investigated as a means of uncovering if clinically evident atherosclerotic vascular disease in CKD patients is linked to endothelial function abnormalities (Thambyrajah *et al.* 2000). The study consisted of twenty-six healthy participants and eighty individuals suffering from chronic renal failure with each group similar in regards to gender and age characteristics. Two indices of endothelial function were assessed: high resolution ultrasonography to measure flow mediated endothelium dependent dilatation of the brachial artery following reactive hyperaemia, and plasma concentration of von Willebrand factor. Endothelial dysfunction was identified in those with chronic kidney failure including individuals with only minor kidney inefficiency. These abnormalities were independent of differences in known vascular risk factors and vessel size between the two groups and suggest that chronic renal failure may directly induce endothelial dysfunction, thereby promoting the development of atherosclerosis. It is also possible that clinically silent atheroma is already present in most patients with renal failure by the time of presentation.

f) Vein Diameter as a marker for AVF Maturation

Endothelial function is associated with arterial and venous remodelling; this finding is associated with basic haemodynamic principles (Owens *et al*. 2010). As more

blood is delivered through the venous outflow limb of the AVF, wall shear stress, proportional to the amount of blood flow velocity and lumen diameter, will rise. Theoretically, this should lead to venous dilation to normalize the shear stress. There is a high degree of correlation between the flow rate through an AVF and the venous diameter indicating that flow is a primary determinant of final venous diameter (Owens *et al*. 2010; Wedgwood *et al.* 1984). It is likely that the magnitude of remodelling depends on the hemodynamic stimuli, endothelium-derived mediators, and the baseline stiffness of the vessels.

The inadequate vessels used to construct AVFs have been identified as another cause of AVF failure. Allon and Robbin (2002) have proposed the use of pre-surgery ultrasound assessment to ensure that the vessels chosen can support the construction of AVF. Zadeh *et al.* (2012) conducted a cross-sectional study using a sample of 96 haemodialysis patients, all of them with native AVF to determine the relation between diameter and maturation of AVF. Study results found an association between the vein diameter and the success rate of fistula development; however, a similar connection was not observed between the fistula maturation and the artery diameter.

g) Diabetes as a marker for AVF Maturation

The most preferred type of vascular access used for haemodialysis is AVF (UK Renal Registry Report 2011; USRDS 2008). Nevertheless, there has been an increase in the rate of AVF failure in the last three decades caused by the growing number of elderly CKD patients, who also suffer from diabetes or vascular disease. Diabetes has become the major determinant of blindness, kidney failure, and leg amputation in

most countries (ADA 1998). In addition, diabetics are more likely to develop peripheral vascular disease, particularly if they are also smokers or suffer from hypertension and hypercholesterolemia.

As noted by Aronson *et al.* (1996), the changes in metabolism that accompany diabetes can manifest as pro-thrombotic situation, damage to the endothelium, deregulation of growth factors and increase in extracellular matrix deposition. Inflammation can participate in the initial development of AVF stenosis and thrombosis (Marrone *et al.* 2007; Chang *et al.* 2005).

Endothelial dysfunction has been explained by Deanfield *et al.* (2005) as a disproportion between the amount of vaso-dilatory and vaso-constricting substances generated by the endothelium or between the general endothelial activities. Endothelial dysfunction can either be a part of the mechanisms of a number of diseases, including diabetes mellitus, hypertension, hypercholesterolaemia, or arise from these diseases or due to environmental factors, such as exposure to air pollution and smoking tobacco products (Cai and Harrison 2000). The deregulation of the endothelium manifests as decreased production of nitric oxide, increased platelet aggregation, and anticoagulant features (Al-Isa *et al*. 2010). All these aspects have a role in the occurrence of vascular problems in diabetics, such as atherosclerosis.

A key component of AVF maturation is adequate dilation of the outflow vein. Changes in blood flow induce vascular remodelling and the response to flow changes is controlled by the endothelium (Dammers *et al*. 2005; Ene-Iordache *et al*. 2003). Upon damage to the vein during the AVF construction, the endothelium is disturbed, succeeding to impair venous remodelling. A retrospective analysis (Conte *et al*.

2011) was performed on the 31 AVF patients to identify factors that may influence AVF remodelling. The results indicated that diabetes is a significant, negative predictor of venous remodelling. However, the sample size was small and thus the significance of the findings may be questionable.

h) Hypertension as a marker for AVF Maturation

Risk factors such as cardiovascular disease, hyperlipidaemia, and hypertension poorly predict AVF non-maturation, prompting investigations into other risk factors such as hemodynamic profile or vessel morphology (Kharboutly *et al*. 2007). Endothelial function is impaired in hypertension (Stefano *et al*. 2001) which decreases vascular relaxation and initiate inflammatory cell infiltration and slight inflammation in blood vessels (Satoh 2012). Macrophages and T cells represent the basic pathological features of the development of atherosclerosis. From their initial location in elastic arteries in spaces that do not come under extreme shear stress, these features are propagated to the innermost membrane of the smooth muscle cells where they lay down connective tissues and initiate neovascularisation (Griendling and Alexander 1994).

Other studies, however, did not support hypertension as a major risk factor for AVF maturation (Kim *et al*. 2011; Lauvao *et al*. 2009). A recent study by Kim *et al*. (2011) performed a single centre cohort study (38 men and 12 women) to assess patients' factors, diameter and distensability of the radiocephalic vein at the wrist. Study analysis did not find any positive correlation between AVF maturation and patients' factors (that is hypertension, diabetes, and gender). However, the sample

size was not large enough to detect the effect between AVF maturation and hypertension.

i) PVD as a marker for AVF Maturation

The prevalence of PVD in people suffering from diabetes is four times higher than those without diabetes (Gregg *et al.* 2004). PVD has developed gradually as a result of systemic atherosclerosis and represents one of the three main symptoms which characterise atherothrombosis, together with coronary artery disease and cerebrovascular disease (Hiatt *et al*. 1995). Atherothrombosis manifests as a thrombus that develops on top of a ruptured plaque situated at an afflicted part of the artery. Atherosclerotic plaques also form at vessel bifurcation point, possibly because of damaged protection mechanisms and disruptions in the flow of blood at these sites (Warboys *et al*. 2011).

In the case of AVF used for haemodialysis access, vessel thrombosis represents the major factor, which determines AVF failure. Chang *et al.* (2005) argued that vascular inflammation may participate in this process, as it represents a significant symptom of vascular diseases. Ku *et al*. (2006) recruited 43 pre-dialysis patients awaiting AVF creation for the first time to compare the intima media thickness of the vessels among uraemic patients, uncomplicated hypertensive patients and healthy subjects by using ultrasonographic measurements. Study findings reported that intima media thickness measurements during preoperative Doppler ultrasound imaging correlated significantly to histologic measures and, more importantly, to AVF thrombosis and to inadequacy of an AVF to maintain dialysis at one year. Similarly, a single centre, cross sectional study of 225 patients was conducted to evaluate the relationship

between ankle-brachial pressure index (ABPI) < 0.9 and vascular access failure. Study findings showed that ABPI is a reliable marker for peripheral vascular disease and has a significant association with access failure after adjusting for other variables (Chen *et al*. 2009). However, the study subjects were included only in one regional hospital and thus the selection of patients was limited and the design of the study is observational, therefore it is susceptible to selection bias.

j) Smoking as a marker for AVF Maturation

Churchill *et al.* (1992) and Reilly *et al*. (1982) have analysed the influence of smoking history on vascular access morbidity but did not obtain any conclusive results. Wetzig *et al*. (1985) had earlier shown that smokers undergoing haemodialysis exhibited an increased prevalence of early or late AVF failure. The discrepancies observed in the results could be attributed to the fact that earlier peripheral vascular impairment in former and current smokers can trigger acute AVF obstruction. Ozdemir *et al*. (2005) examined the effects of smoking and blood eosinophil count AVF maturation. This cross-sectional study included 141 patients with advanced renal failure. AVF thrombosis was detected in 60 patients; in contrast, 81 patients had no thrombosis. The study findings strongly indicate that smoking in conjunction with a high amount of blood eosinophils can play a role in the occurrence of AVF failure. One of the limitations of the study was that it was retrospective and limited to a single centre.

In addition, progression of atherosclerosis and ischaemic nephropathy may play a part as well (Ritz and Orth 2000). Endothelial dysfunction can be accompanied by factors, which increase the likelihood of development of atherosclerosis, including

oxidized lipids, diabetes mellitus, and smoking (Brunner *et al.* 2005; Wilson 2004; Hackam and Anand 2003; Madore 2003; Shimokawa 1999). Endothelial dysfunction generates a number of biological effect, that aids the advancement of atherosclerosis, such as vasoregulation (Landmesser *et al.* 2004; Widlansky *et al.* 2003; Keaney 2000), enhanced blood coagulation (Bombeli *et al.* 1997), facilitating the penetration of inflammatory cells and lipids into the innermost wall layer (Schwartz *et al.* 1999), and enhancing the movement and multiplication of vascular smooth muscle cells (Raymond *et al.* 2004).

k) Obesity as a marker for AVF Maturation

The number of obese ESRD patients, who also are diagnosed with type 2 diabetes, is experiencing a constant growth (Postorino *et al.* 2009). This group of patients are associated with a higher rate of AVF failure as they are predisposed to arteriosclerosis and the vessels in the forearm are more difficult to reach due to thick fat tissue (Kats *et al.* 2007). This also increases the difficulty of performing phlebotomy on the fistula situated at a considerable depth. Chan *et al.* (2008) carried out a retrospective cohort study on a group of 1486 patients to analyse the connection between obesity and vascular access complications, using BMI of less than 30 kg/m^2 as reference for obesity. The study results found that there was no connection between obesity and a higher rate of fistula failure; however, a relation between insufficient fistula development and a high BMI was observed (Odd Ratio 3.66, 95% CI-1.27–10.55, $p = 0.017$). Because this study represents the fistula outcomes from a single dialysis centre, the findings may not generalize to all dialysis centres. For

example, in centres not using routine preoperative vascular mapping, the frequency of fistula placement may be lower in obese, as compared to non-obese patients.

Generally, in the case of patients who are obese, diabetics, of female sex, older than 65 years, or patients who suffer from vascular diseases, native AVF is constructed to provide access for haemodialysis (Weyde *et al.* 2008; Allon *et al.* 2000). In obese patients, low rates of long-term AVF preservation are usually caused by early vessel thrombosis, which is considered to degenerate from advanced myointimal hyperplasia, determining an earlier occurrence of vessel stenosis. The theory is corroborated by the fact that a connection has been found between hyper insulinaemia and high levels of serum interleukin 6, and advanced myointimal hyperplasia, as well as an increased incidence of vessel thrombosis in patients undergoing haemodialysis (De Marchi *et al.* 1996). Interleukin 6 stimulates the production of C-reactive protein, high levels of which have been recorded in obese patients (Ramkumar *et al.* 2004). In addition, Kuji *et al*. (2005) revealed that C-reactive protein contributes to the advancement of myointimal hyperplasia, which provides further evidence in the high rate of AVF failure in obese patients.

l) Dialysis as a marker for AVF Maturation

Late referral of patients initiating dialysis therapy with a temporary CVC can impair the patency rate and fistula maturation. If the fistula is constructed after the patient has begun the dialysis therapy it could lead to the extension of the haemodialysis treatment with the temporary CVC, which could determine the development of a number of complications, such as insufficient blood flow, haematoma formation, recurrent thrombosis or failure, fibrosis and vessel wall damage and bacteraemia

(Ravani *et al.* 2004; Avorn *et al.* 2002; Roubicek *et al.* 2000; Schwab and Beathard 1999).

Previous studies examined the complications related to central venous catheter use before AVF construction and have reported venous thrombosis rates as high as 58%, with a susceptibility for thrombosis in the cephalic and basilic vein (Abdullah *et al.* 2005; Allen *et al.* 2000). Through a prospective observational study results have shown that a temporary catheter used at the initiation of dialysis is linked to a higher risk of vascular access failure (Rayner *et al.* 2003). The authors hypothesized that AVF patency rates and maturation could be influenced by catheter utilisation and related problems. This research used a substantial study sample of dialysis patients (n=3674) and involved an epidemiological study that took place in over 300 institutions across Europe, in America and in Japan. However, as pointed out by the authors themselves, because of an observational study, it is not possible to make a causal link between cannulation and catheter utilization and subsequent fistula failure.

CHAPTER 3

METHODOLOGY

3.1 Research Design

This is a single centre exploratory study, to evaluate the effect of blood markers and risk factors in the prediction of maturation of AVF. This study has been divided into two parts. In the first part a regression model was developed on retrospective data of 300 patients, who had undergone vascular access surgery (AV Fistula) between 2006 and 2009 in Royal Infirmary of Edinburgh. In the second part (prospective) data of 100 newly recruited participants, who had undergone the surgical procedure (AVF creation), was used to validate the model developed from retrospective data. This method of development and validation of prediction model was adopted to estimate the probability of developing a particular outcome in the future (prognosis) as in our study, maturation or non-maturation of AVF (Collins *et al.* 2011; Mallett *et al*. 2010). The purpose of developing a model was not intended to replace clinical judgment, prediction models have a clear role in strengthening clinical judgment. Studies have shown prediction models provide more accurate and less variable estimates of risk compared to more subjectively made predictions (Kattan *et al*. 2013; Ross *et al*. 2002).

Before considering whether to use a clinical prediction model, it is essential that its predictive performance be empirically evaluated in datasets that were not used to develop the model (Steyerberg *et al.* 2013; Altman *et al*. 2009). This is referred as external validation (Steyerberg *et al.* 2009). Performance is typically characterised by evaluating a model's calibration and discrimination (Kuehn 2013). Reasons for assessing performance in other datasets include quantifying optimism from model over fitting or deficiencies in the statistical modelling during model development and

evaluating the transportability of the model in different locations consisting of plausibly similar individuals (different case-mix). External validation is exploring genuine differences in characteristics of the cohorts (between the development and validation cohorts) and examining how well the model performs.

3.2 Sample Size

The goal was to explore associations between maturation of arteriovenous fistula (dependent variable) and biomedical variables (independent variables) in predicting fistula maturation. Maturation of fistula can be determined by predictive logistical regression models that may become imperative tools to estimate patient outcome probabilities (mature/immature AVF). Sample size analysis is a key component in designing a statistical study. It investigates the optimal allocation of study resources to increase the likelihood of the successful achievement of a study objective. For binary logistical regression, effective sample size can be estimated by the number of events or non-events (van Houwelingen and le Cessie 1990).

The proportion of events (failure of the fistula to mature adequately to support dialysis therapy) is approximately 50% (Mendes *et al*. 2002) with 100 sample data that may mean that this would provide only 50 events. It is thought that, a minimum of 100 events and 100 non-events are suggested to obtain adequate power in the development of model. The power of a statistical test is the probability of rejecting the null hypothesis in favour of an alternative hypothesis when the alternative hypothesis is true (Maxwell *et al*. 2008). Samples with around 100 events had approximately 80% power to identify significant variations in model performance (Vergouwe *et al*. 2005). Prognostic models do not always work well in practice, as

often they are too optimistic, so it is extensively suggested that they need to be validated in patients other than those from whose model was developed (Altman and Royston 2000).

The external validity of a model does not only depend on the development process of the model, but also on the new patients for whom the model is applied. A total of 400 participants were recruited, with two thirds (300, retrospective) for model development and one third (100, prospective) for the model validation (Stone 1974).

3.3 Ethical Approval

This study was reviewed and given favourable ethical opinion by the South East Scotland NHS Research Ethics Committee, NHS Research and Development and the Queen Margaret University ethics committee (Appendix I).

3.4 Informed Consent

Patient's participation in this research was entirely voluntary. Written informed consent was obtained from all study participants and those not capable to provide an informed consent have been excluded (Appendix II). All ethical guidelines were met to ensure the safety and well-being of the participants and the researcher. A detailed information sheet was prepared to provide the patients all the information required in order to make an informed decision regarding participation in the project (Appendix III). Participants were aware that they can withdraw from the study at any point, without giving a reason and the withdrawal did not affect their treatment in any way.

3.5 Retrospective Study (Development of Prognostic Model)

Retrospective study was performed systematically in different steps from identification, screening, recruitment, data collection of potential participants and finally data analysis by using appropriate statistical test (Figure 9)

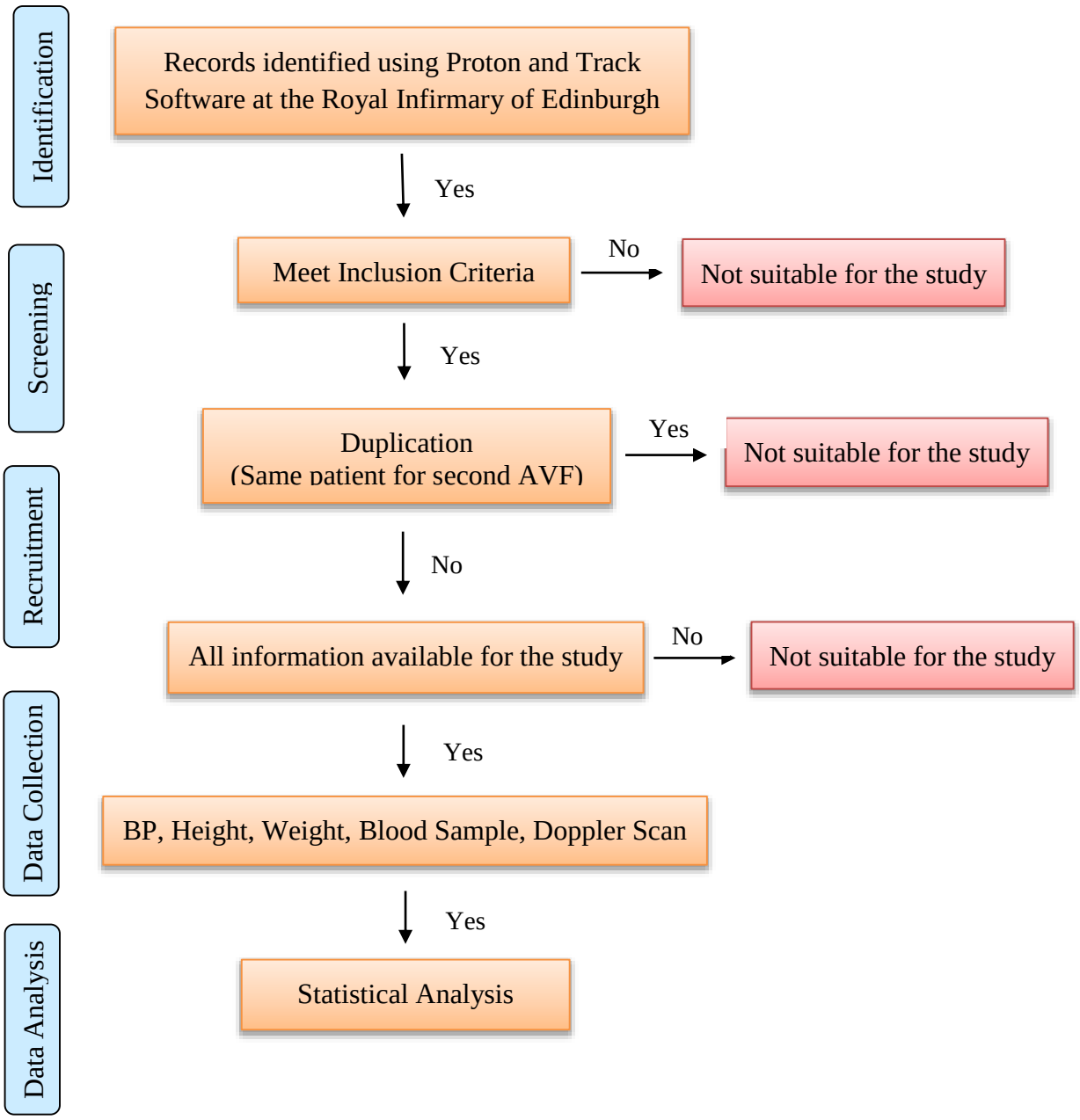


Figure 9. Flow Diagram Showing Steps of Retrospective Study

3.5.1 Recruitment of Participants

The vascular access nurse specialists provided significant help in identifying the potential candidates to the research project. The potential participants were carefully chosen by the researcher on the basis of inclusion and exclusion criteria from those who underwent vascular access surgery at the Royal Infirmary of Edinburgh.

Initially, a list detailing patients who had undergone vascular access surgery was obtained from vascular access nurse specialists. Purposive sampling technique was used for patient's recruitment. A retrospective case note review was performed on all patients identified from the hospital vascular access database as having undergone construction of AVF. The medical case files of the patients who had undergone fistula surgery between 2006 and 2009 were retrieved from the medical records (Proton® software, and Apex® software) at the Royal Infirmary Edinburgh. At the beginning all potential participants' records were screened comprehensively. From the data, reports of patients were developed from the pre-operative assessment papers and the clinical results of their operation obtained from the clinical records and follow up case notes.

A total of 1008 fistula were constructed during the period. From these 300 cases having first time AVF creation and 708 patients were excluded due to incomplete information in relation to the fistula outcomes or those already undergone prior AVF creation.

3.5.2 Inclusion Criteria

- Aged 18 years and older.
- Both genders (Male/Female) were eligible for the study.
- Patients diagnosed with end stage renal disease.
- Patients underwent AV fistula creation at the Royal Infirmary of Edinburgh.

3.5.3 Exclusion Criteria

- Patients who had undergone a repeat AVF creation (2nd and further fistula creations)

3.5.4 Outcome Measures

The portfolios of the measures to be used were:

3.5.4.1 Demographics

In this study patient age, gender, surgeon, type of fistulae, dialysis therapy before AVF creation has been included in the analysis as previous research found their association with the maturation of AVF. A number of studies supported worse AV fistula patency rates in elderly versus non-elderly patients (Obialo *et al*. 2003; Ridao-Cano *et al*. 2001; Burt *et al.* 2001). Increased age has been associated with increased intima-media thickness associated with AV fistula failure (Kim *et al*. 2006).

In the HEMO Study, female sex was identified as a significant predictor of graft rather than AVF use (Allon *et al.* 2000). Results of a retrospective study reveals that female gender is one of the risk factor for fistula maturation failure (Rodriguez *et al*.

2000). However, a meta-analysis of eight prospective and 30 retrospective studies did not reveal statistically significant differences in gender and age (Rooijens *et al*. 2004).

In a systematic review of 34 studies, primary patency rates of upper arm fistulae were approximately 81% compared with 71% in forearm fistulae (Huber *et al*. 2003). Although AVF failure rates have varied slightly from study to study and across patient populations, forearm fistulae in particular are well documented as failing to mature at rates greater than that of upper arm fistulae (Huber *et al*. 2003; Miller *et al*. 2003). In spite of this, forearm fistulae remain the primary vascular access of choice due to relative ease of creation and preservation of proximal vasculature for future access attempts.

Moreover late nephrology care is associated with frequent use of short-term central venous catheters, whose complications may increase the risk of arteriovenous fistula failure, especially due to central venous stenosis and early cannulation of the native vascular access (Ravani *et al*. 2005). A case-control study was conducted to assess the association between past peripherally inserted central catheters and lack of functioning AVFs in 282 (El Ters *et al*. 2012). Study results found a strong and independent association between peripherally inserted central catheters use and lack of a functioning AVF (OR, 3.2; 95% CI, 1.9 – 5.5; $p < 0.001$).

3.5.4.2 Risk Factors (DM, HTN, PVD and Smoking)

Diabetes is a well-known risk factor for vascular disease and arteriosclerosis. Leapman *et al.* (1996) concluded that patients with diabetes are at risk of poor outcomes with the arteriovenous fistula. Konner *et al*. (2002) found AVF survival similar to that of nondiabetic patients. However, steal syndrome was more common in the diabetic group. Maturation of AVFs was found to be worse with hypertension patients in recently published studies (Kaygin *et al*. 2012; Palmes *et al*. 2011). After the fistula creation, vessel calcifications were detected in diabetics and hypertensive patients, leading to arteriosclerosis and thickening of the arterial wall (Erkut *et al*. 2006; Chin *et al*. 2004).

The presence of peripheral vascular disease has been associated with an increased risk of AVF failure. Ku *et al*. (2006) reported that intima media thickness measurements during preoperative Duplex ultrasound imaging correlated significantly to histologic measures and, more importantly, to AVF thrombosis and to inadequacy of an AVF to maintain dialysis at 1 year. Similarly, ankle-brachial pressure index, a reliable marker for peripheral vascular disease, had a significant association with access failure after adjusting for other variables (Chen *et al*. 2009).

Multiple studies have suggested that smoking has the negative effect on the AVF maturation (Monroy-Cuadros *et al*. 2010; Gheith and Kamal 2008; Wetzig *et al*. 1985). A cross-sectional study included 141 patients to determine the effects of smoking and blood eosinophil count on the development of AVF thrombosis. Study indicated that smoking and high blood eosinophil count contribute to the development of AVF thrombosis (Ozdemir *et al*. 2005).

3.5.4.3 Kidney Function Tests (Na, K, Ca, HCO_3, Urea, Creatinine, eGFR)

The kidney function test which examines that the kidneys are working correctly, measures the level of uraemic toxins in the blood such as urea, creatinine, eGFR and electrolytes (Na^+, K^+, Ca^{++} and HCO_3). High levels of uraemic toxins may reduce endothelial and cardiac function worsening blood flow to the vascular access (Ravani *et al*. 2004). A recent retrospective cohort study, to test uraemia as a predictor of AVF maturation in 16 patients with advance kidney disease concluded that uraemia is not a predictor of time-to-AVF maturation or primary patency failure (Pannu and Misra 2012). However, the number of subjects was minimal and research utilising a bigger study group is required.

3.5.4.4 Coagulation Profile (PT and INR)

Early failure of fistulas due to thrombosis or inadequate maturation is a barrier to increasing the prevalence of fistulas among patients with end stage renal disease. The time required for coagulation to take place is known as prothrombin time. The shortness of time is determined mainly by prothrombin concentration. The International Normalised Ratio (INR) is a ratio of the persons PT to a normal control sample raised to the power of international sensitivity index (International Committee for Standardisation in Haematology 1985).

Recent retrospective analysis of results of AVF created for haemodialysis in CRF patients suggested that judicious use of antiplatelet/anticoagulant agents in cases of AVF for haemodialysis access can be beneficial in preventing the chances of occlusion of AVF and thus helps in its long term patency (Yogi *et al*. 2012). A

randomized, double-blind, placebo controlled trial was conducted at nine US centres composed of academic and community nephrology practices in 2003-2007 (Dember *et al*. 2008). Eight hundred seventy-seven participants with end stage renal disease or advanced chronic kidney disease were followed up until 150 to 180 days after fistula creation. Study results showed that Fistula thrombosis occurred in 53 (12.2%) participants assigned to clopidogrel compared with 84 (19.5%) participants assigned to placebo (relative risk, 0.63; 95% confidence interval, 0.46-0.97; $p = 0.018$).

3.5.4.5 Lipid Profile (TC, HDL and TG)

Findings of previous studies revealed a close relationship between vascular access thrombosis and hyperlipidaemia as indicated by higher values of cholesterol, triglycerides, low-density lipoprotein cholesterol and lower values of high-density lipoprotein cholesterol (Serati *et al.* 2007; De Marchi *et al*. 1996). Moreover, results of a retrospective study suggested that not total cholesterol, but lipid subfractions (LDL and HDL) were associated with AVF thrombosis (Kirkpantur *et al*. 2008).

3.5.4.6 Vein Diameter

Multiple studies were published that report good or improved AVF outcomes achieved with the use of pre-operative ultrasound. Almost all report a higher rate of AVF in preference to arteriovenous grafts (AVG) and better primary patency AVF (McGill *et al*. 2005; Nguyen *et al*. 2003; Ascher *et al*. 2000). A Meta-analysis of preoperative Duplex ultrasound vessel diameters for successful AVF placement revealed that the use of Duplex ultrasound is important in determining preoperative

vessel diameter size, and subsequent functional success rate of fistula placement (Glass *et al*. 2009).

3.5.4.7 Body Mass Index

In prospective study including patients receiving a first fistula or graft during a 2-year period the access outcomes were compared between obese (BMI ≥ 30 kg/m^2) and non-obese (BMI < 30 kg/m^2) patients (Kats *et al*. 2007). Study results showed obesity was the only significant factor predicting secondary fistula failure (hazards ratio 2.93; 95% CI, 1.44–5.93; p = 0.004). However, Chan *et al*. (2008) examined AVF outcomes for 1486 haemodialysis patients and compared those with a BMI < 30 *versus* > 30 kg/m^2 but were unable to confirm BMI as a factor in predicting AVF revision or failure. However, an increased risk of failure to mature was identified for those patients with BMI > 35 kg/m^2.

3.5.5 Data Collection

The details of patient's factor and blood markers were explored by complete review of the patient's inpatient and outpatient medical record (containing all information pertaining to medical and surgical consultations and all previous hospital admissions and management) via an electronic database. All the data was entered into an Excel spreadsheet (Microsoft, USA). The following variables were collected:

- Demographic including age, gender and risk factors; peripheral vascular disease; diabetes mellitus; hypertension; smoking (ever versus never) and dialysis (ever versus never) were collected. Fistulae characteristics that were ascertained include fistulae type and side of the arm.

- Measurement of brachial artery blood pressure and the participant weight and height was retrieved. Patients were defined as obese when their body mass index was greater than 30 Kg/m^2, consistent with the World Health Organization classification (2014).
- Clinically important biomedical markers, estimated glomerular filtration rate; Serum Urea; Creatinine; Potassium; Sodium; Calcium; Bicarbonate; Prothrombin Time; International Normalization Ratio; High Density Lipoprotein; Triglyceride; Total Cholesterol and Vein diameter were obtained
- Results of Duplex investigation of the veins (measure the diameter of arm veins) was also recorded.

3.6 Prospective Study (Validation of Prognostic Model)

The prospective study was performed systematically in different steps from identification, screening, recruitment, data collection of potential participants and finally data analysis by using appropriate statistical test (Figure 10).

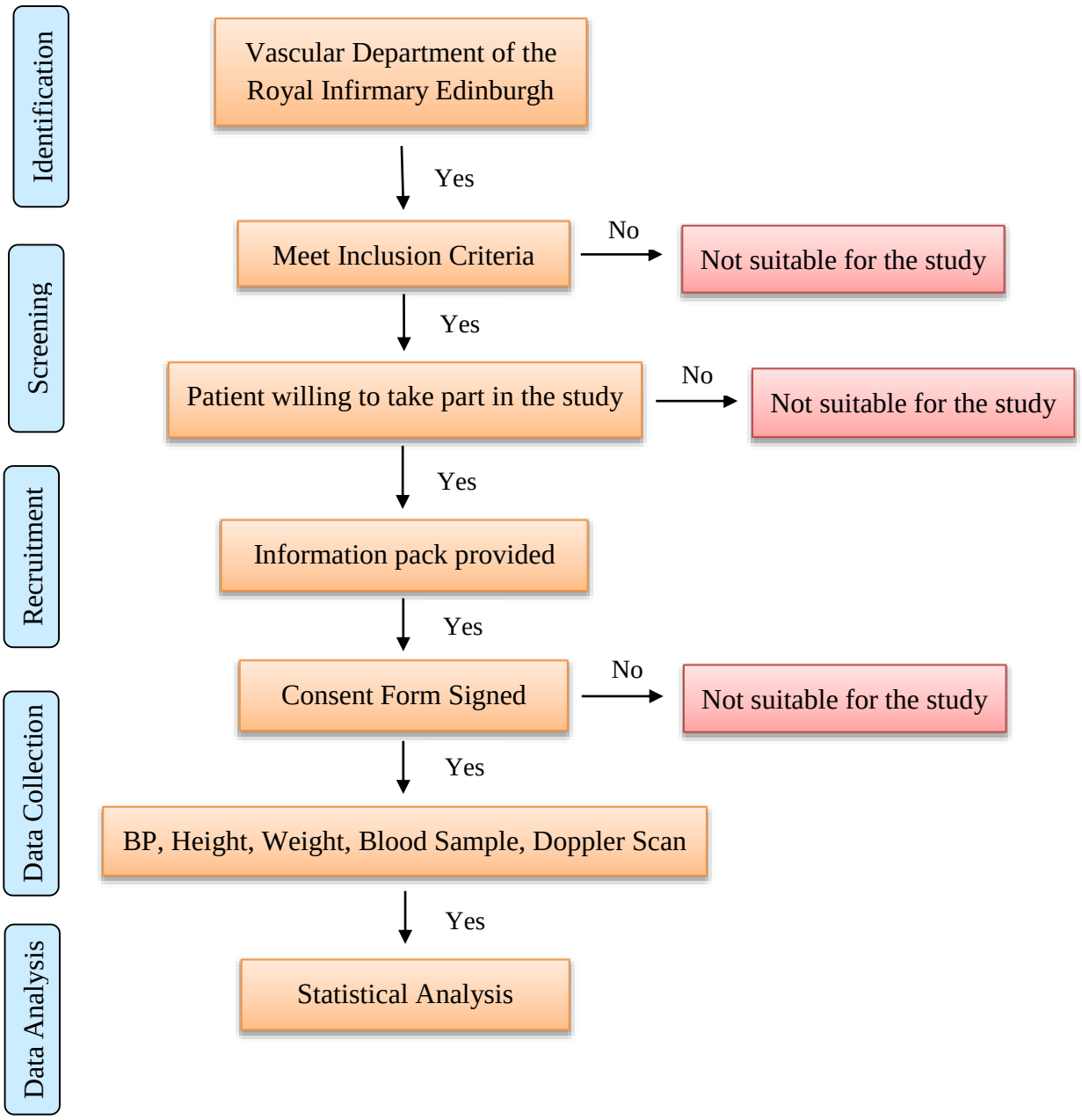


Figure 10. Flow diagram showing steps of prospective study

3.6.1 Recruitment of Participants

The recruitment process occurred at the vascular department in the Royal Infirmary of Edinburgh. The vascular consultants and vascular access nurse specialists provided significant help in identifying the potential candidates to the research project. The potential participants were chosen by the consultant vascular surgeon and the vascular access nurse specialists on the basis of inclusion and exclusion criteria as the patients came into the hospital for vascular access surgery.

The initial approach to the patient and their parent/carer occurred during the routine appointment in the vascular department. The patients were introduced to the researcher by the vascular consultants. The recruitment process for this study began by providing verbal information about the study. If the patient appeared to be interested, then an information pack containing a comprehensive information sheet and a consent form was provided to the patients. After one week, the researcher contacted the patients, to answer any further enquiries and to take back the completed consent form if they agreed to participate in the study. The participant information leaflet contained the contact information of the investigator and independent advisor, if the patients wished to discuss the study further (Appendix 1).

A total of 168 patients were contacted for prospective clinical research who had undergone surgery for AVF at the Royal Infirmary of Edinburgh between the years 2009 and 2011. Out of the 168 patients contacted for this trial, 23 were unwilling to participate in this trial, 10 drop out at follow-up and 35 were excluded from the study because they did not meet the inclusion and exclusion criteria. The most often cited reason for a patient not being willing to participate was personal commitments.

Moreover, excluded patients includes non-native English speakers (unable to give informed consent) and second attempt of AVF creation. Thus, a total of 100 patients were recruited into the prospective study.

3.6.2 Inclusion Criteria

- Aged 18 years and older.
- Both genders (Male/Female) were eligible for the study.
- A projected life expectancy of > 6 months.
- A projected/ diagnosed ESRD with expected initiation of haemodialysis within six months of enrolment, or current dialysis dependence.
- A planned procedure for first time arteriovenous fistula creation.
- The patient was supposed to receive dialysis at the Royal Infirmary of Edinburgh facility for at least three months.
- Ability to give informed consent.

3.6.3 Exclusion Criteria

- Pregnancy or breastfeeding.
- Bleeding diathesis.
- Illness/ Inability to give informed consent.
- Involvement in another medical trial.
- Expected on-compliance with medical care.
- Current unstable angina or uncontrolled diabetes
- Participant’s refusal.

3.6.4 Data Collection

After taking informed consent, patient assessments were conducted on the day of their Duplex investigation. All procedures were carried out by the regular NHS staff. However, in order to make sure the patients data was collected according to standard NHS operating procedures, the researcher was present at all times. The assessment process was conducted as follows:

- The participant had the chance to ask questions and raise any issues before, during, and after each assessment.
- Baseline demographic information was collected including age, gender, previous history of dialysis and risk factors such as diabetes, hypertension, peripheral vascular disease and smoking.
- A general physical examination consisted of inspection and palpation of the vessels of the upper arm and forearm and measurement of brachial artery blood pressure. Subsequently, height and weight details were recorded in order to calculate the BMI values by a nurse. For the assessment, participants were required to remove their outer clothing so the weight and height were accurately recorded.
- Participants' blood samples were obtained. For the participants blood analysis approximately 10 ml of blood was obtained by inserting a needle into a vein in the arm. Blood samples were obtained by NHS staff, as a regular procedure for pre-operative tests. From the blood analysis, kidney function status, coagulation profile, and lipid profile were calculated. The blue bottle is used for haematology tests involving the clotting system, which require inactivated whole blood for

analysis (Figure 11). Bottle contains buffered sodium citrate, which acts as a reversible anticoagulant by binding to calcium ions in the blood and subsequently disrupting the clotting cascade. Sodium citrate is also added to blood products for transfusion, and acts as a preservative by stopping them from clotting in the bag.

Figure 11. Blue bottle used for haematological tests

- Figure 12 shows yellow bottle that was used for test requiring separated serum for analysis, including urea, creatinine and electrolytes (Na, K, Ca) and lipid profile (TC, HDL, TG). This bottle is known in the lab as the serum separating tube. It contains two agents; silica particles and a serum separating gel. The silica particles work to to allow the blood to clot fully. The serum separator consists of an inert polymer gel which floats as a layer between the blood cells and plasma to form a physical barrier between them. This means that the sample can be centrifuged (spun) in the laboratory and the separated serum easily removed.

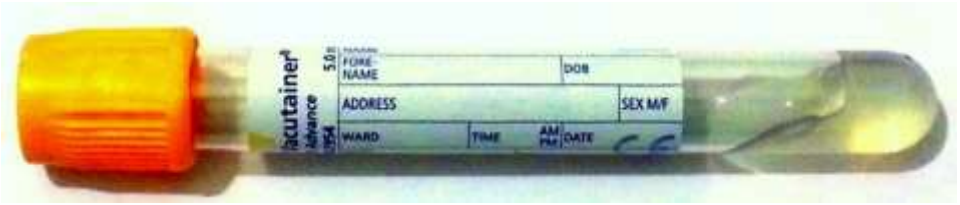


Figure 12. Yellow bottle use for kidney function test and lipid profile

- Duplex investigation of the veins was performed to measure the diameter of arm veins according to a standard protocol by vascular access nurse specialists.

3.7 Statistical Analysis

In the retrospective study a total of 300 participants were recruited for the prognostic model development. Descriptive statistics were produced giving mean and standard deviation for demographic data. The association between dependent variables and independent variable were assessed utilising univariate logistical regression. An important note to consider is that the pre-selection of predictors based on univariate statistical significance is arbitrary. It is a better choice to make use of previous research and expert opinion for the first selection of predictors without relying too much on statistical pre-selection alone. From a set of 300 patient's data, the following set of clinically important predictors of mature fistulae were identified:

Kidney Function Test

- estimated Glomerular Filtration Rate (eGFR)
- Blood Urea
- Creatinine
- Serum potassium (K^+)
- Sodium (Na^+)
- Calcium (Ca^{++})
- Bicarbonate (HCO_3)

Coagulation Test

- Prothrombin Time (PT)
- International Normalization Ratio (INR)

Lipid Profile

- Total Cholesterol (TC)
- Triglyceride (TG)
- Low Density Lipoprotein (LDL)
- High Density Lipoprotein (HDL)

In addition to these biomedical markers demographic data were analysed.

- Age
- Body Mass Index (BMI)
- Vein Diameter
- Diabetic status
- Hypertension (HTN)
- Peripheral Vascular Disease (PVD)
- Dialysis (ever *versus* never)
- Smoking status (ever *versus* never)

Statistical analysis was performed using SPSS (IBM *SPSS* Statistics 20.0). Data are expressed as mean and 95% confidence interval (CI) or as proportions. Initially, the relationship between each individual predictor was investigated with the outcome measure in a model that only includes the predictor and outcome measure. Univariate

analysis of categorical variables by Chi square test was performed. This was to establish which of the risk factors differed significantly between fistulae of mature to needle and those that failed to mature (inadequate for dialysis). The association between independent variables and dependent variable, mature fistula, was assessed utilising univariable logistic regression. The criteria for a variable to enter the model was $p < 0.25$.

Regression model was used for the prediction of AVF outcome. There are different types of regression modelling.

- Linear Regression (if outcome variable is continuous)
- Multinomial Logistic Regression (if outcome variable is more than two)
- Logistic Regression (if outcome variable is binary or dichotomous)
- Cox regression model (can be used for a "time to event" model)

Logistic regression is used to analyse relationships between a dichotomous dependent variable and metric or dichotomous independent variables. Logistic regression does not make any assumptions of normality, linearity, and homogeneity of variance for the independent variables. Because it does not impose these requirements, it is preferred to discriminant analysis when the data does not satisfy these assumptions

The equation for simple linear regression is:

$$Y = a + bx + e_i$$

Where y-outcome, a- intercept, b- slope related to x (explanatory variable), e- error term or random noise.

$$Y = logit\ (p) = a + bx + e_i$$

$$\log(\frac{p}{1-p}) = a + bx + e_i$$

The regression equation estimated by logistic regression is given by:

$$\log\left(\frac{p}{1-p}\right) = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ldots\ldots + \beta_n X_n$$

Where p is the probability of event and effect of independent variable (x) increase or decrease risk of this event. β_0 is the intercept and β_1 till β_n are the regression coefficients.

A model was developed utilising multivariable stepwise logistic regression with the variables found to be significant from the univariable regressions. In backward selection all the selected variables were initially entered at the same time into a model. Subsequently the variables with the highest p-values were manually removed (i.e. those variables contributing the least). Then the model was re-run. This step was repeated until all the variables left had a p-value smaller than 0.05. The odds ratios and associated 95 per cent confidence intervals for variables in the final predictive model were obtained. We considered a *p* value less than 0.05 to be statistically significant.

Logistical regression models often experience serious multi collinearity problems resulting from strong correlations between independent variables. Correlations among the independent variables included, were investigated to avoid multi colinearity. The criterion for removal for variable exhibiting multicolinearity was correlation coefficient > 0.7. Once a final model was derived, model performance was assessed by both calibration and discrimination.

Performance of Prognostic Model

Once a prognostic model has been developed, there is a need for it to be investigated to find out how well the model works; in other words how well does the model predict outcomes (mature or immature AVF)? The Hosmer-Lemeshow test was used to investigate how well the predicted probabilities agree with the observed probabilities. This test should not be statistically significant, *p* value greater than 0.05 showing that the model fits the data. A better way of assessing the fit of a logistic regression model is to compare the expected and observed numbers of positives for different subgroups of the data. If the observed and expected numbers are sufficiently close, then we can assume that we have an adequate model.

ROC curve was generated to determine the discriminatory power of the model to differentiate between mature and immature AVF, which range from 0 to 1. A value of 0.5 means that the model is useless for discrimination (equivalent to tossing a coin) and values near 1 means that higher probabilities will be assigned to cases with the outcome of interest compared to cases without the outcome. To generate the ROC, we have to save the predicted probabilities from the model. The larger the AUC, the better the diagnostic test. If the area is 1.0, the test is "ideal" because it achieves 100% sensitivity and 100% specificity. If the AUC is 0.5, then you have a test that has effectively a 50% sensitivity and a 50% specificity, which is no better than flipping a coin (Brubaker 2008). The area under the ROC curve for a prognostic model is typically between 0.6 and 0.85 (Royston *et al*. 2009). Sensitivity and specificity analysis were reported. Sensitivity is the proportion of the true positive outcomes (e.g., truly diseased subjects) that are predicted to be positive. Specificity

is the proportion of the true negative outcomes (e.g., truly disease-free subjects) that are predicted to be negative.

Validation of Developed Model

The validation of model is the most important part of developing a prediction rule. In other words, validating the model explores how well predictions generated by the prognostic model agree with predictions for future patients or comparable patients not part of the study population. Predictive logistic regression models are important tools to provide estimates of patient outcome probabilities (Vergouwe *et al*. 2005).

In general, there are two forms of validation. The first, internal validation, is performed in the context of an individual study, for example by splitting the study data set into one data set to build the model (development set) and one data set to test performance (test set, also called the validation set). The appealing feature of internal validation is its convenience, as it does not require collection of data beyond the original study. The second, external validation on a different data set provided by a different study circumvents these issues. Validation on heterogeneous external data sets allows for evaluation of the generalizability of the risk prediction tool to wider populations than originally reported.

A total of 100 participants were recruited for the model validation phase. A model precisely predicting probabilities for patients in the retrospective data would not guarantee accurate predictions for new patients from related populations, e.g. patients treated not long ago or patients from a different centre, therefore, the performance of prognostic models needed to be verified in the newly treated patient group (external

validation) (Harrell *et al*. 1996). External validation was performed on those data obtained from an independent set of consecutive patients who had undergone vascular access surgery using the final development model. Predicted probabilities for individual patients in the validation set were calculated. Model discrimination was assessed by ROC curve analysis. Evaluation of calibration is important if model predictions are used for making clinical decisions. A calibration plot formed by the Hosmer-Lemeshow test, which illustrates how the observed and expected proportions compare, assessed the calibration of the final model for the maturation of the fistula.

3.8 Data Protection

All information about participants collected during the study was secure and was accessible only to the research team members. A 'master copy' of individual identification numbers unique to each participant was stored in a safe place in the vascular department at the Royal Infirmary of Edinburgh and was accessible only to the named key investigators/collaborators. This identification number corresponded with the participant's personal details and any participant information material and consent forms. This number was used throughout the research of the study to correspond with any scientific data collected, no personal and identifying information were used. All data was collected by the chief investigator throughout the study, access to data was only to the key investigators and associated collaborators.

Data was collated and stored electronically on the designated research laptop hard drive and back-up discs. The laptop and back-up discs were password protected,

including the master copy of participants identification numbers (stored in a separate secure location within the vascular lab at Royal Infirmary of Edinburgh). Patients' confidentiality was paramount during the dissemination of findings and submission of manuscripts for publication. The published literature did not include any names other than basic demographic data such as subject number, age, sex, height etc. Written documentation and data were also stored in a paper format in the participant's medical notes as per normal clinical practice.

The storage and subsequent destruction of data are compliant with the Data Protection Act 1998. Written documentation and data have been stored in a paper format in the participants' medical notes as per normal clinical practice. These will be destroyed after 5 years following discharge as per the health care records policy. All forms of data were securely kept in locked cabinets within locked rooms. Only the principal investigators and associated members had permission to use and access. All information that was collected during the course of the research were kept strictly confidential. All data was anonymised as much as possible, and the participant would not be identifiable from any of the data collected. Participant's names were exchanged with a number and it would not be possible to be identified individually.

3.9 Indemnity

If participants had any reservations about any aspect of this study, they could seek help from the investigator. Alternatively, they could also contact the independent advisor (contact details given), who knows about the project but is not directly involved in this research.

Royal and Sun Alliance insurance provides indemnity for QMU sponsored or co-sponsored clinical study (Appendix IV). This is a no-fault compensation policy and covers any person taking part in a clinical trial including their dependants, executors, heirs, administrators and legal representatives. Cover applies automatically to clinical trials and general clinical research within wide parameters without the need for referral although there are exclusions. In this study no complaints were received.

3.10 Validity and Reliability

3.10.1 Measurement of Body Mass Index

The Body Mass Index (BMI) represents the standard method used by both the World Health Organisation (WHO) and the governmental health sectors of the majority of nations to determine whether a person is obese or overweight. The BMI is determined by dividing the weight of an individual by his/her height measured in metres and quared. If the BMI is below 30 kg/m^2, the individual is not obese; if the BMI exceeds 30 kg/m^2, then the individual is considered to be obese. The height of the participants was determined with the use of a portable instrument composed of a vertical measuring board and a horizontal headboard, known as a stadiometer. This entailed the participants having to take their shoes off and stand against the vertical board with the knees straight and the heels touching each other. Additionally, the head had to be in the anatomical position, known as the Frankfurt Plane, meaning that the head has to be positioned in such a way that an imaginary line going through the upper border of the ear canal and the lower margin of the orbit would run parallel to the ground, as shown in Figure 13. The stature of the participant was measured in

metres with a metre/height scale with the participant in standing position without their shoes and socks.

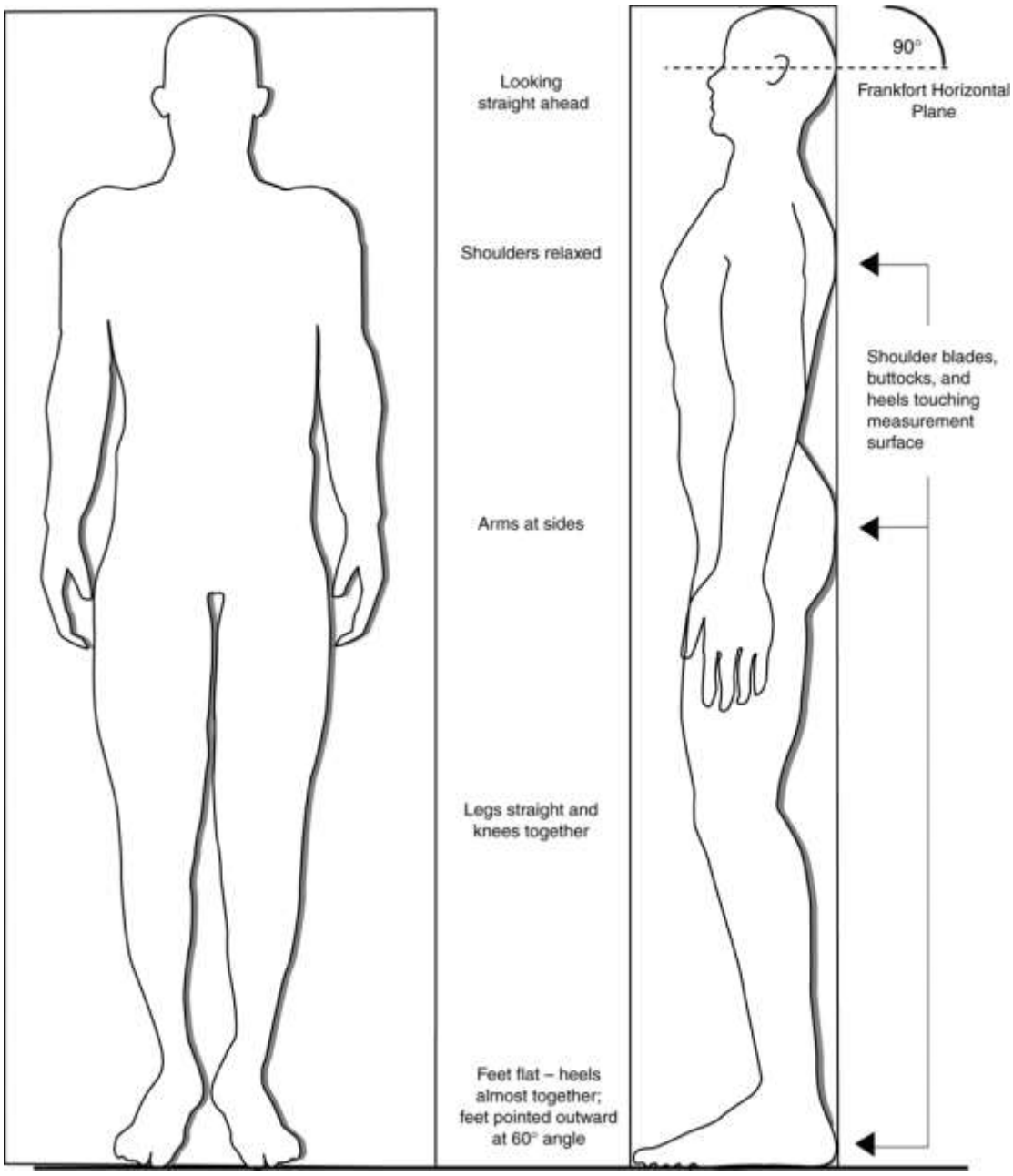


Figure 13. Positioning of participant when measuring height. (NHANES 2007)

The weight of the participant was measured on a weighing scale of range suitable to the participant's size. It was ensured that the scales were at zero. Accuracy of the scale was checked using standard weights. The participant's shoes and outer clothing

was removed prior to weighing and participants were weighed in minimum clothing where possible. Weight reading was recorded in kilograms with the participant standing still.

3.10.2 Measurement of Blood Pressure

Prior to the measurement of the blood pressure, each participant was allowed to rest in an average room temperature (20-25 ^{0}C) for ten minutes, the inflatable cuff of the sphygmomanometer, which was adjusted to fit each participant, being positioned on the left upper arm in such a way as to be 2 to 3 cm above the ante-cubital vein. Furthermore, the arm was laid on a flat surface to ensure that the cuff was aligned with the heart.

- Small Cuff (16-23cm)
- Medium Cuff (24 - 36cm)
- Large Cuff (37 - 45cm)
- Extra Large Cuff (45 - 60cm)

In accordance with Beevers *et al.* (2001) and Perloff *et al.* (1993), the procedure was explained to the participants in order to provide reassurance in the event that their blood pressure was initially high.

Sphygmomanometer

There are three types of sphygmomanometer – light, dial and mercury-based. Before each procedure, it must be verified that the sphygmomanometer is on zero and that the monitor readings are clear. A number of studies (Markandu *et al.* 2000; Nolan and Nolan 1993; Petrie *et al.* 1986) have indicated that almost half of the existing sphygmomanometers are not precise, thus there is a high possibility that their

readings are incorrect. In order to verify the accuracy of the instruments, whether or not they fulfil the required standards, maintenance or recalibration tests have to be carried out every year by biomedical technicians. Petrie *et al.* (1986) also specified that the date of the most recent calibration has to be recorded.

The component parts of the inflatable cuff – bladder, tubes, inflation bulb, and valves – have to be checked to ensure that they function properly. Cuffs made of nylon have to be disinfected after every use. Cuffs made of fabric have to be washed on a regular basis.

The bladder has to be long enough to envelop the arm of an individual and has to be positioned in such a way so that its central part lies above the brachial artery. This prevents 'cuff hypertension', which could cause incorrect blood pressure readings (Beevers *et al.* 2001).

With regards to breadth, the cuff bladder is normally two-thirds of the total length of the upper arm of an adult, from the proximal end of the ulna, the olecranon process, to the acromion process of the shoulder blade, the scapula. As emphasised by de Swiet *et al.* (1989), the dimensions and placement of the cuff are highly important elements that contribute to the precision of the blood pressure readings.

3.10.3 Biochemistry Tests

Assessment of the lipid profile, and kidney function test was undertaken at the Clinical Biochemistry Laboratory, Royal Infirmary of Edinburgh, Scotland, UK, using an Olympus AU2700 automated analyser. (Note Olympus® has been subsequently taken over by Beckman®).

Serum Urea

Kinetic UV test was used to calculate the serum urea. Through hydrolysis, urea is decomposed into ammonia and carbon dioxide. In the presence of glutamate dehydrogenase, the ammonia reacts with α-oxoglutarate and NADH, producing glutamate and NAD. The change in absorbance of the solution (caused by the oxidation of NADH) is measured photometrically at 340nm.

Kinetic UV, Cat No OSR6534

Calibrator Olympus system Calibrator 66300

Reference Range 2.5-6.6mmol/L

Serum Sodium (Na^+) and Potassium (K^+)

Analysis of electrolytes in whole blood was performed using potentiometric ion selective electrode (ISE) of Beckman Coulter AU analyser at the Royal Infirmary of Edinburgh. All electrolytes are measured simultaneously within a single chip.

Calibration 66320 ISE buffer

66317 ISE Low serum Std

66316 ISE High serum Std

66313 ISE Na^+ / K^+ Selectivity check

Na^+- Reference range 135-145 mmol/L

K^+- Reference range 3.6-5.0 mmol/L

Bicarbonate (HCO_3)

Latex immunoassay whereby agglutination of antigen-antibody complexes causes a change in absorbance at 572 nm.

Olympus System CRP Latex reagent

Calibrator (Normal set: ODC 00026, highly sensitive set: ODC 00027)

Cat No OSR6199

Ref Range 17-23 mmol/L

Serum Creatinine

To make sure that the non-haemolysed serum samples used have attained stability (to allow the blood to clot fully), they are kept for two or more days at a room temperature of between 18 to 25°C or for seven days at a temperature of between 2 to 8°C. Standard kinetic Jaffe method was used to calculate the serum creatinine rate of absorbance change measured photometrically at 500nm. The Olympus System calibrator, connected to the National Institute of Standards and Technology Standard Reference Material, was employed to measure the reaction.

Kinetic Jaffe, Cat No OSR6178

Calibrator 66300

Reference range 60-120 umol/L

Calibration frequency is more difficult. The electrolytes are calibrated daily or as required and most other tests probably monthly. Creatinine is weekly and HbA1c only with column changes or if required by troubleshooting.

Total Cholesterol (TC)

Enzymatic reaction involving cholesterol esterase. Formation of a coloured dye is measured photometrically at 500nm.

Enzymatic colour test, Cat No OSR6116

Calibrator - Olympus System Cal 66300

Reference Range - 5.0 mmol/L or less

HDL Cholesterol

Uses a detergent to solubilise HDL, which then reacts with other compounds to form a coloured dye, measured photometrically at 604 nm.

Enzymatic colour test: Cat No OSR6187

Calibrator HDL cholesterol calibrator ODC0011

Reference Range 1.1-1.7 mmol/L

Triglyceride

Enzymatic reaction involving glycerol phosphate oxidase. Formation of a red dye is measured photometrically at 500 nm.

Enzymatic colour test: Cat No OSR6118

Calibrator: 66300

Reference Range 0.8-2.1mmol/L

3.10.4 Measurement of eGFR

An effective way of assessing how well the kidneys are functioning is to calculate the glomerular filtration rate (GFR). The GFR is a calculation of the amount of waste fluids in millilitres filtered by the kidneys in one minute. Thus, the GFR indicates the functioning state of the kidneys. It has been estimated that kidneys, which function properly, can filtrate over 90 ml/min/1.73 m^2 of blood per minute.

Only a formula-based estimation of the GFR can be obtained. Due to the fact that a precise direct measurement of the eGFR is not possible, only a formula-based estimation of the GFR can be obtained, which is known as eGFR. Generating this estimation entails the determination of the amount of waste product termed creatinine present in a sample of blood; demographic factors, such as age, gender, and ethnicity, have to be born in mind when conducting this test. The outcome is equated with the functioning percentage of healthy kidneys, so that if, for instance, the eGFR is 50 ml/min/1.73 m^2 it means that the functioning capacity of the kidneys is 50% (Harris and Stribling 2007).

In order to estimate the GFR, the equation of isotope dilution mass spectrometry (IDMS) with modification of diet in renal disease (MDRD) was used, based on creatinine assays compared against standard accredited material.

Calculation of GFR uses MDRD (Modification of Diet in Renal Disease Study Group) equation (Traynor *et al.* 2006).

$$\boldsymbol{Estimated\ GFR\ (ml/min/1.73m2)\ = 186.3\ \times (Creatinine/88.4)\text{-}1.154\ \times (Age)\ –\ 0.203\ \times (0.742\ if\ female)\ \times (1.210\ if\ black)}$$

The creatinine assays should be definite and unbiased when contrasted to IDMS. If non-specific assays are used, such as the Jaffe assessments, are employed and certain adjustment elements have to be applied to reduce the variation in the results obtained by different laboratories. The laboratory processing of the blood samples was carried out within 12 hours after they were collected.

3.10.5 Coagulation Screen

Prothrombin time and INR was measured at the Clinical Laboratory, Royal Infirmary of Edinburgh, using ACL TOP 700 coagulation analyzer, Instrumentation Laboratory (IL), UK (Reagent: HemosIL Recomboplastin 2G IL UK).

The normal range of prothrombin time calculated was 10.5 - 13.5 seconds. The analysers themselves were validated prior to installation. Each analyser is validated for PTs/ INRs when a new lot of thromboplastin reagent is introduced, prior to the current batch running out. The laboratory at the Royal Infirmary of Edinburgh established the mean normal PT using healthy volunteers and then go on to determine the international sensitivity index (ISI) of the reagent using WHO calibrant. This is further validated by running Internal Quality Control (IQC) and External Quality Control (EQC).

Routine operation of the analysers involves IQC being performed post daily maintenance procedure and every 6 hours after this or when a vial of thromboplastin is changed. Tests cannot be performed if the IQC fails. IQC was performed using a normal and abnormal sample control, to ensure that a method is under control at different levels of an analyte, since relatively minor changes in an analytical process may be more apparent when testing an abnormal control. This means that within

limit QC results can confirm that the method is under control for both normal and abnormal sample analysis. QC sample tests was performed with normal levels and one further level where the result is outside the reference range.

EQC involves registration with United Kingdom National External Quality Assessment Service (UK NEQAS). UK NEQAS facilitates optimal patient care by providing a comprehensive external quality assessment service in laboratory medicine which sends out several surveys at regular intervals throughout the year.

3.10.6 Measurement of Vein Diameter

All participants underwent routine preoperative vascular mapping. The Duplex scan was a non-invasive method of obtaining pictures of the veins of the arm. The technique used sound waves to construct a scan. Ultrasound scan was performed by vascular access nurse specialists at the Royal Infirmary of Edinburgh in the presence of the researcher. Vascular access nurse specialists looked specifically at the patient's upper limb. The test required patients to be lying down and involved the placement of a small device on the skin of the arm. Ultrasound gel was used to improve the quality of the scan. The gel acts as both a lubricant and an energy conductor. The purpose of the gel is to convey the acoustic energy (sound waves) from the ultrasound head (transducer) to the tissue without crossing through the air at any point. A transducer is a handheld pointer that looks very much like a small microphone. When the transducer is rubbed along the skin, a picture of the inside of the body begins to emerge on the ultrasound monitor. Whilst the patient was lying down, each limb was examined. It was not necessary to use a tourniquet to make the veins more visible, as this was achieved with an ultrasound scan device (Siemens

with 5-MHz, 7-MHz, or 10-MHz scanning probes). The axillary and subclavian veins were examined to rule out outflow obstruction. The non-dominant arm is always selected first as if any complication occur post-surgery, the dominant arm is preserved. The ultrasound scan imagining device enabled the calculation of the vein diameter at eight important locations (wrist, distal, mid and proximal forearm, and anterior area of the elbow, distal, mid and proximal arm) as indicated in Figure 14. With regards to quality standards, the Medical Physics Department at the Royal Infirmary of Edinburgh conducted a yearly examination of the ultrasound scan device with the use of an ultrasound phantom to make sure of correct calibration.

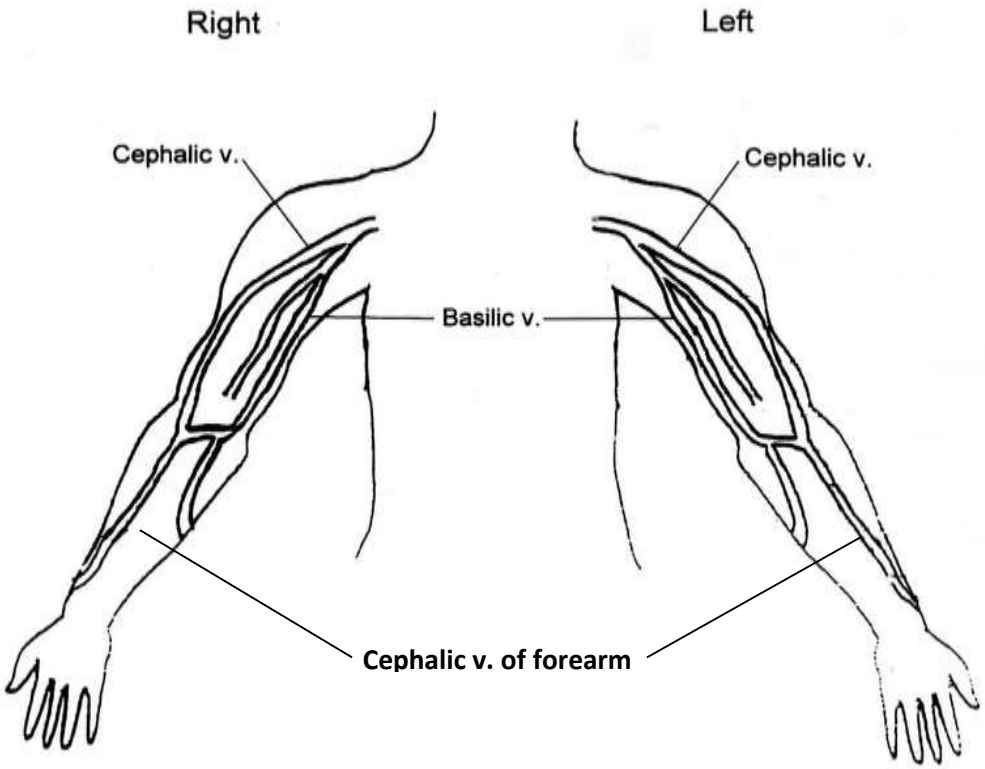


Figure 14. Upper extremity vein mapping (Adapted from Mendes *et al*. 2002)

3.11 Maturation of Fistula

Maturation refers to the possibility of ensuring continuous operative haemodialysis at six weeks after the creation of a fistula (Patel *et al*. 2003). The decision as to when the fistula was ready to undergo the process of cannulation, as well as the actual process, were made by dialysis specialist nurse with substantial practical experience. If the process failed, the vascular surgeon at the Royal Infirmary of Edinburgh carried out a reassessment of the fistula.

CHAPTER 4

RESULTS

4.1 Descriptive Statistics

A search of the renal unit electronic patient record (Proton® and Apex® software) at the Royal Infirmary of Edinburgh was conducted to identify all patients who had vascular access operations between the years 2005 and 2009. A total of three hundred patients were identified of whom 200 (66.7%) were male and 100 (33.3%) were female.

In this study population, age ranged from 19 to 87 years, with a mean age of 60.45 ± 15.9 years. Of the 300 AVF procedures performed, 73.7% (n = 221) were created in the left arm and 26.3% (n = 79) were created in the right arm. Percentage of patients found to have diabetes was 38% (n = 114) and smokers were 13.7% (n = 41). There were 78% (n = 234) of patients had history of hypertension and 16% (n = 48) of the participants were known case of peripheral vascular disease. Prior to AVF creation 37.3% (n = 112) of study participants had haemodialysis through temporary venous catheter or arteriovenous graft. Nearly one third (n = 80) of study participants had BMI greater than 30. More than a half (62.7%) participants had received brachiocephalic AVF, 27% (n = 81) had received radiocephalic AVF and in 10.3% (n = 31) of the participants brachiobasilic AVF was created. General distribution of independent predictive variable for maturation of AVF are shown in Table 6.

Table 6. Distribution of Independent Predictive Variable for Maturation of AVF

Clinical characteristics	n (300)	% Total	Clinical characteristics	n (300)	% Total
Arm			**Creatinine (µmol/L)**		
Left	221	73.7	≤ 120	3	1
Right	79	26.3	>120 to ≤400	163	54.3
Fistula			>400	134	44.7
B/C	188	62.7	**Urea (mmol/L)**		
R/C	81	27	≤ 6.6	47	15.7
B/B	31	10.3	>6.6 to ≤15	56	18.6
Surgeon			>15	197	65.7
Surgeon A	204	68.0	**eGFR**		
Surgeon B	75	25.0	**(mm/min/1.73m^2)**		
Surgeon C	7	2.3	≤15	190	64.6
Surgeon D	5	1.7	>15	109	35.4
Surgeon E	9	3.0	**SBP (mm Hg)**		
PVD			≤130	159	53
No	252	84	>130	141	47
Yes	48	16	**DBP (mm Hg)**		
DM			≤85	272	90.7
No	186	62	>85	28	9.3
Yes	114	38	**BMI (Kg/m^2)**		
Smoker			≤30	220	73.3
No	259	86.3	>30	80	26.7
Yes	41	13.7	**PT (seconds)**		
HTN			≤13.5	260	86.7
No	66	22	>13.5	40	13.3
Yes	234	78	**INR**		
Dialysis			≤1.2	264	88
No	188	62.7	>1.2	36	12
Yes	112	37.3	**TC (mmol/L)**		
K^+ (mmol/L)			≤ 5	228	76
> 5	137	45.7	>5	72	24
≤ 5	163	54.3	**TG (mmol/L)**		
Na^+ (mmol/L)			≤ 2.1	190	63.3
< 135	44	14.7	>2.1	110	36.7
≥ 135	256	85.3	**HDL (mmol/L)**		
Ca^{++} (mmol/L)			≤ 1.1	153	51
≤ 2.5	261	87.0	>1.1	147	49
> 2.5	39	13.0	**Vein Size (mm)**		
HCO_3(mmol/L)			≤2.5	38	12.7
≤ 23	135	45	>2.5	262	87.3
>23	165	55			

Independent patient factors and blood markers distribution in the subgroups. Data values are expressed as number and percentage (%). n- number of participant, B/C-Brachiocephalic, R/C- Radiocephalic, B/B- Brachiocephalic, PVD-Peripheral Vascular Disease, DM-Diabetes Mellitus, HTN-Hypertension, K-Potassium, Na-Sodium, Ca-Calcium, HCO_3-Bicarbonate, e-GFR- Estimated Glomerular Filtration Rate, SBP- Systolic Blood Pressure, DBP- Diastolic Blood Pressure, BMI- Body Mass Index, PT-Prothrombin time, INR- International normalized ratio, TC- Total Cholesterol, TG- Triglyceride, HDL- High density lipoprotein.

4.1.1 Gender and AVF Maturation

Out of 200 male participants, 120 (60%) developed mature fistula and in 80 (40%) participant's fistula failed to mature (Table 7, Figure 15). Significant difference (p = 0.005) was observed between mature and immature AVF among male gender. On the other hand, 48 (48%) of fistulas had matured in 100 female participants. No significant (p = 0.68) difference was observed between mature and immature AVF among female gender. Success of AVF maturation was found to be associated (p = 0.048) with male and female gender (Table 7).

Table 7. Gender and Maturation Rate of Fistula

	Mature	**Immature**	**Total**	**Chi-Square**	***P* value**
Female	48	52	100		
Male	120	80	200	3.896	0.048
Total	168	132	300		

Table 7 shows the distribution and relationship between outcomes of AVF surgery (mature or immature) and Gender. The p value = 0.048 indicating that AVF surgery outcomes was dependent of the patients gender.

Figure 15. Gender and AVF Maturation

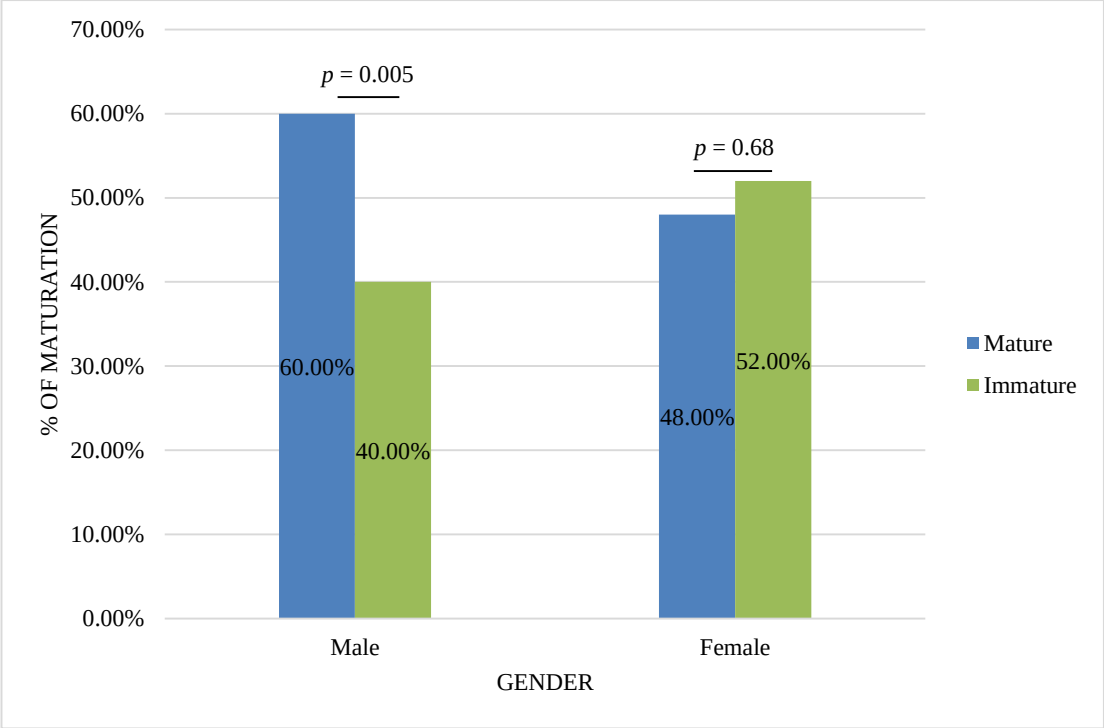


Figure 15 showing relationship between success and failure of AVF maturation among male and female gender who had undergone AVF surgery. Numbers written within the bar indicated the percentage and black line over the bars indicates level of statistical significance (Chi square) between mature and immature AVF among male and female gender.

4.1.2 Right or Left handed AVF and Maturation

Out of 300 patients, 221 (73.7%) had left sided and 79 (26.3%) received right sided fistulae (Table 8). Maturation of the AVF was successfully attained in 50 (63.3%) procedures and 29 (36.7%) fistulae failed to mature in the right sided AVF. Significant difference (p = 0.02) was observed between mature and immature AVF among right sided AVF. In contrast 118 (53.3%) fistula successfully matured and 103 (46.6%) failed to mature in the left arm (Figure 16). No significant difference (p = 0.313) was observed between mature and immature AVF among left sided AVF. Success of AVF maturation was found to be independent (p = 0. 128) of arm selected for procedure (Table 8).

Table 8. Maturation in Left or Right Sided AVF

	Mature	**Immature**	**Total**	**Chi-Square**	***P* value**
Right	50	29	79		
Left	118	103	221	2.314	0.128
Total	168	132	300		

Table 8 shows the distribution and relationship between outcomes of AVF surgery (mature or immature) and side of arm (right or left). The p value = 0.128 indicating that AVF surgery outcomes was independent of the arm selected.

Figure 16. Maturation of Left /Right Sided AV Fistula

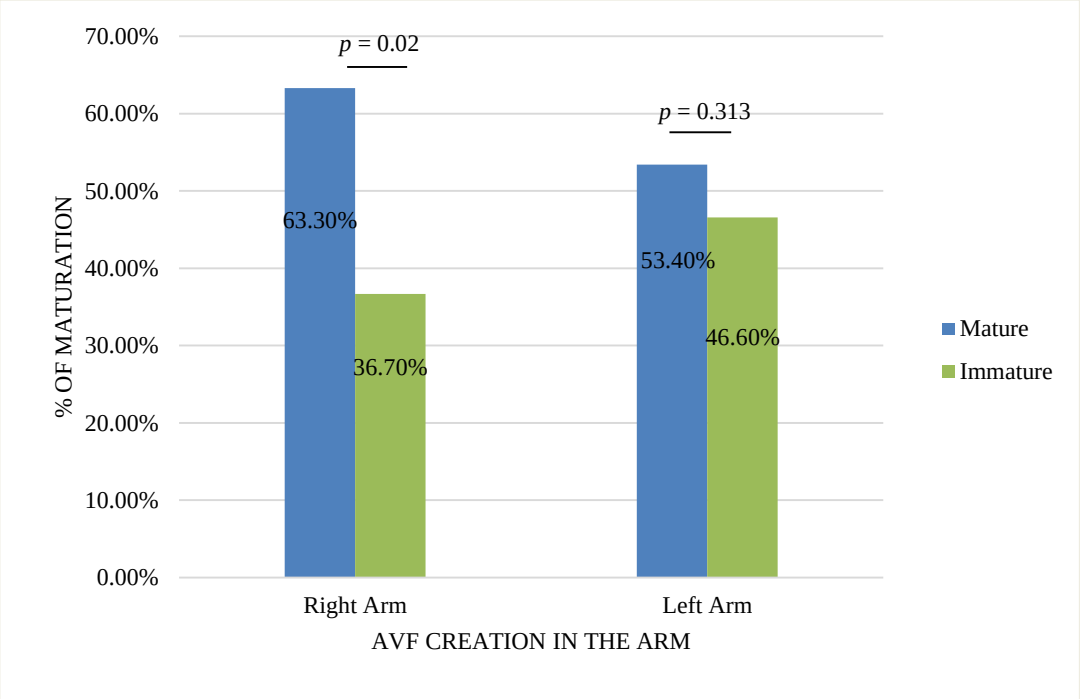


Figure 16 showing relationship between success and failure of AVF maturation in right sided and left sided vascular access. Numbers written within the bar indicated the percentage and black line over the bars indicates level of statistical significance (Chi square) between mature and immature AVF created in right or left side of patients arm.

4.1.3 Type of Fistula and Maturation

Of 300 participants included in the study, 188 (62.7%) received a brachiocephalic AVF, 81 (27%) received a radiocephalic AVF, and 31 (10.3%) received a brachiobasilic AVF (Table 9). Maturation of the AVF was successfully accomplished in 113 of the BC AVF (60.1%), 42 of the RC AVF (51.9%) and 13 of the BB AVF (41.9%). Failure rate of the fistulae was 39.9% (n = 75), 48.1% (n = 39) and 58.1% (n = 18) in BC, RC and BB AVF respectively (Figure 17). Significant difference (p = 0.006) was observed between mature and immature AVF among BC AVF. However, no statistical difference was found between mature and immature AVF for RC (p = 0.74) and BB (p = 0.37) AVF. Success of fistula maturation between different sites of AVF (BC, RC and BB) was compared with no statistical difference (p = 0.114) found (Table 9).

Table 9. Type of Fistula and Maturation of AVF

	Mature	**Immature**	**Total**	**Chi-Square**	***P* value**
BC	113	75	188		
RC	42	39	81	4.341	0.114
BB	13	18	31		
Total	168	132	300		

Table 9 shows the distribution and relationship between outcomes of AVF surgery (mature or immature) and type of AVF. The p value = 0.114 indicating that AVF surgery outcomes was independent of the type of AVF.

Figure 17.Type and Maturation of AV Fistula

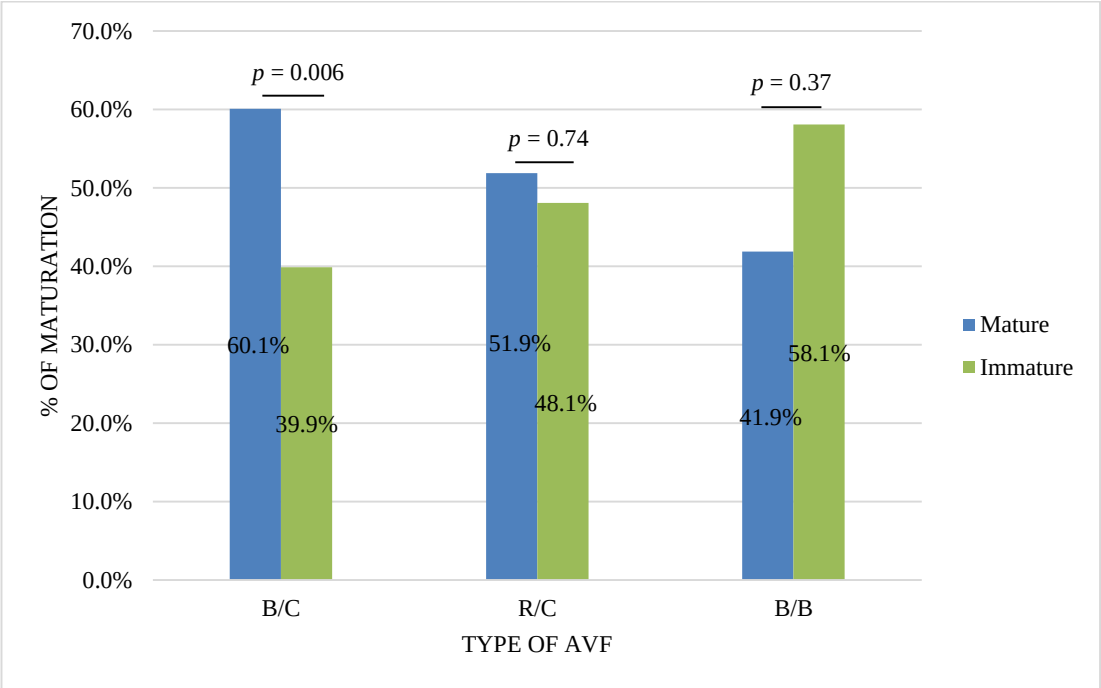


Figure 17 showing relationship between success and failure of AVF maturation in three different types of AVF. Numbers written within the bar indicated the percentage and black line over the bars indicates level of statistical significance between mature and immature AVF among three different AVF (B/C-Brachiocephalic, R/C-Radiocephalic, B/B–Brachiobasilic).

4.1.4 Surgeons and AVF Maturation

Of three hundred participants included in the study, 204 (68%) participants AVF was created under the care of surgeon A, 75 (25%) treated by surgeon B, 07 (2.3%) treated by surgeon C, 5 (1.7%) treated by surgeon D and 9 (3%) treated by surgeon E (Table 10). Out of 204 AVF, created under the care of surgeon A, 115 (56.4%) matured and 89 (43.6%) did not mature. Likewise AVF created by surgeon B, 42 (56%) matured and 33 (44%) did not mature, AVF created by surgeon C, 5 (71.4%) matured and 2 (28.6%) did not mature, AVF created by surgeon D, 2 (40%) matured and 3 (60%) did not mature and fistula created by Surgeon E, 4 (44.4%) matured and 5 (55.6%) did not mature (Figure 18). Significant difference was observed between mature and immature AVF among AVF created by surgeon A ($p = 0.07$) and B ($p = 0.03$). However, no statistical difference was found between mature and immature AVF constructed by surgeon C ($p = 0.26$), D ($p = 0.65$) and E ($p = 0.74$). Nevertheless, due to the small number of procedures performed by Surgeons C, D and E, these results should be interpreted with caution. No significant association ($p = 0.792$) was found between AVF created by different surgeons and successful fistula maturation found (Table 10).

Table 10. Surgeons and Maturation of AVF

	Mature	Immature	Total	Chi-Square	*P* value
Surgeon A	115	89	204		
Surgeon B	42	33	75		
Surgeon C	5	2	7	1.695	0.792
Surgeon D	2	3	5		
Surgeon E	4	5	9		
Total	168	132	300		

Table 10 shows the distribution and relationship between outcomes of AVF surgery (mature or immature) and surgeons performed surgery. The *p* value is 0.792 indicating that outcomes of AVF surgery was independent of the surgeons.

Figure 18. Surgeons and AVF Maturation

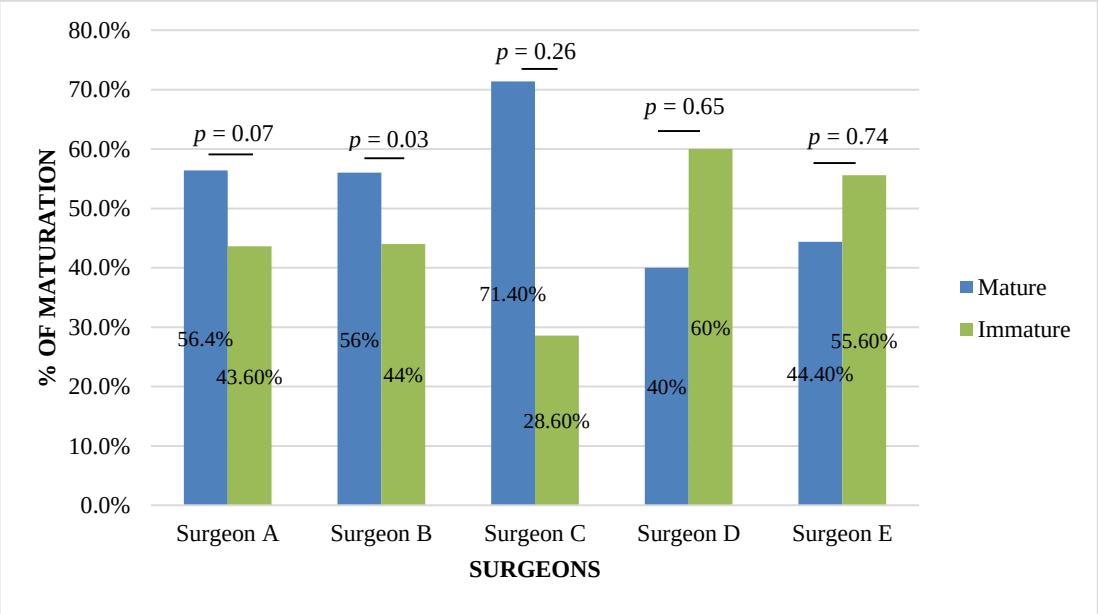


Figure 18 showing relationship between success and failure of AVF maturation created by different surgeons at RIE. Numbers written within the bar indicated the percentage and black line over the bars indicates level of significance (Chi square) between mature and immature AVF created by surgeons in the department of vascular surgery.

4.1.5 Diabetes and AVF Maturation

Out of 300 included participants, there were 114 diabetic patients and 186 non-diabetic patients (Table 11). The researcher did not find any significant differences between outcome measures that are mature and non-maturation of fistulae in diabetic patients. The success rate of fistula in the DM participants was 57 (50%) that of equal with failure rate 57 (50%). In the non-diabetic group 111 (59.7%) achieved mature fistulae and 75 (40.3%) failed to mature. Significant difference (p = 0.008) was observed between mature and immature AVF among non-diabetic population. However, no statistical difference was found between mature and immature AVF in diabetic patients (Figure 19). Success of AVF maturation was not found to be associated (p = 0.128) with diabetic and non-diabetic patients (Table 11).

Table 11. Diabetes and Maturation of Fistula

	Mature	**Immature**	**Total**	**Chi-Square**	***P* value**
Diabetics	57	57	114		
Non Diabetics	111	75	186	2.314	0.128
Total	168	132	300		

Table 11 shows the distribution and relationship between outcomes of AVF surgery (mature or immature) and diabetes. p = 0.128 indicating that AVF surgery outcomes was independent of the presence and absence of diabetes.

Figure 19. Diabetes and Maturation of AV Fiatula

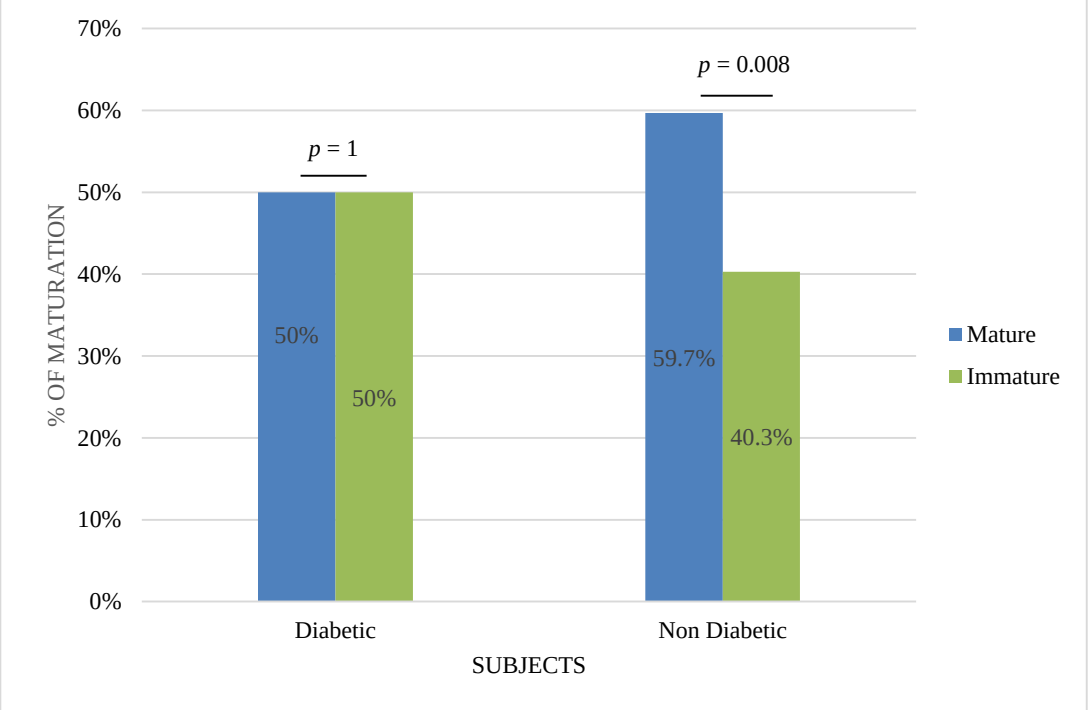


Figure 19 showing relationship between success and failure of AVF maturation in diabetic and non-diabetic participants who had undergone AVF surgery. Numbers written within the bar indicated the percentage and black line over the bars indicates level of significance (Chi square) between mature and immature AVF in patients with diabetes and without.

4.1.6 Hypertension and AVF Maturation

A total of 234 (78%) participants were hypertensive and 66 (22%) were non hypertensive (Table 12). In the hypertensive participants, success of AVF maturation was 57.3% (134) while failure rate was 42.7% (100). On the other hand, 51.5 % (34) AVF matured in non-hypertensive participants and 48.5% (32) failed to mature (Figure 21). Significant difference (p = 0.026) was observed between mature and immature AVF among hypertensive patients. However no significant association (p = 0.8) was found between mature and immature AVF among non-hypertensive patients (Figure 20). Success of AVF maturation was not found to be associated (p = 0.406) with hypertensive and non-hypertensive patients (Table 12).

Table 12. Hypertension and Maturation of Fistula

	Mature	**Immature**	**Total**	**Chi-Square**	***P* value**
Hypertensive	134	100	234		
Non Hypertensive	34	32	66	0.691	0.406
Total	168	132	300		

Table 12 shows the distribution and relationship between outcomes of AVF surgery (mature or immature) and high blood pressure. p = 0.406 indicating that outcomes of AVF surgery was independent of the presence and absence of hypertension.

Figure 20. Hypertension and Maturation of AV Fistula

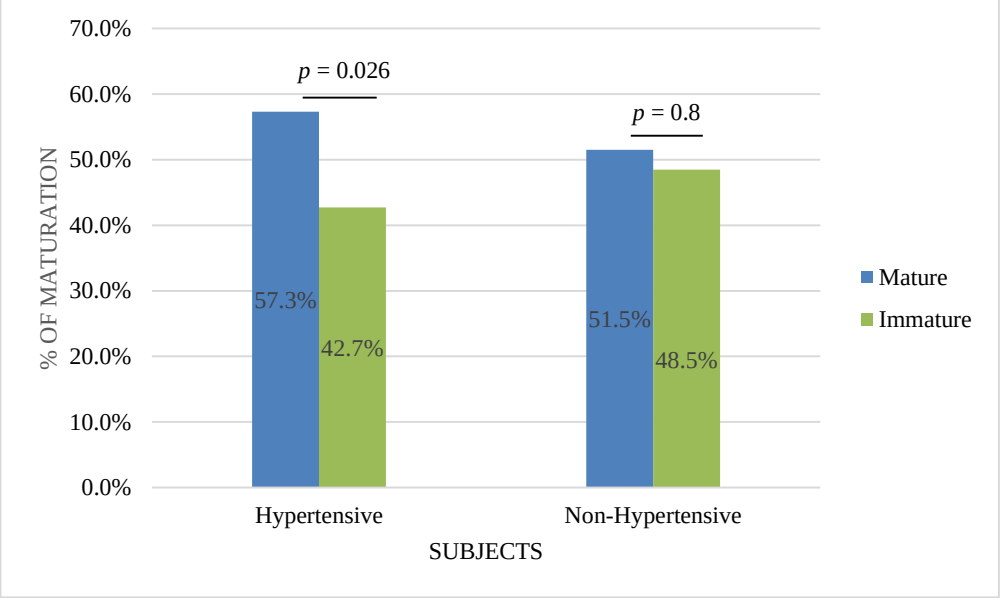


Figure 20 showing relationship between success and failure of AVF maturation in hypertensive and non-hypertensive participants who had undergone AVF surgery. Numbers written within the bar indicated the percentage and black line over the bars indicates level of significance (Chi square) between mature and immature AVF within group of patients with and without hypertension.

4.1.7 PVD and AVF Maturation

Of 300 participants included in the study, 48 (16%) were diagnosed with PVD and 252 (84%) did not have the history of PVD (Table 13). Approximately 33.3% (16) of the study participants with peripheral vascular disease successfully achieved mature fistula and 66.7% (32) failed to mature. Significant difference (p = 0.021) was observed between mature and immature AVF among patients with PVD. In contrast, maturation of AVF among participants with no history of PVD was 60.3% (152) and the failure rate was 39.7% (100) summarized in Figure 21. Significant difference (p = 0.001) was found between mature and immature AVF in patients without history of PVD. Success of AVF maturation was found to be associated (p = 0.001) with the patients with and without a history of PVD (Table 13).

Table 13. Peripheral Vascular Diseases and Maturation of Fistula

	Mature	**Immature**	**Total**	**Chi-Square**	***P* value**
PVD (Yes)	16	32	48		
PVD (No)	152	100	252	11.915	0.001
Total	168	132	300		

Table 13 shows the distribution and relationship between outcomes of AVF surgery (mature or immature) and PVD (Peripheral Vascular Disease). p = 0.001 indicating that AVF surgery outcomes was dependent to the presence and absence of PVD.

Figure 21. PVD and Maturation of AV Fistula

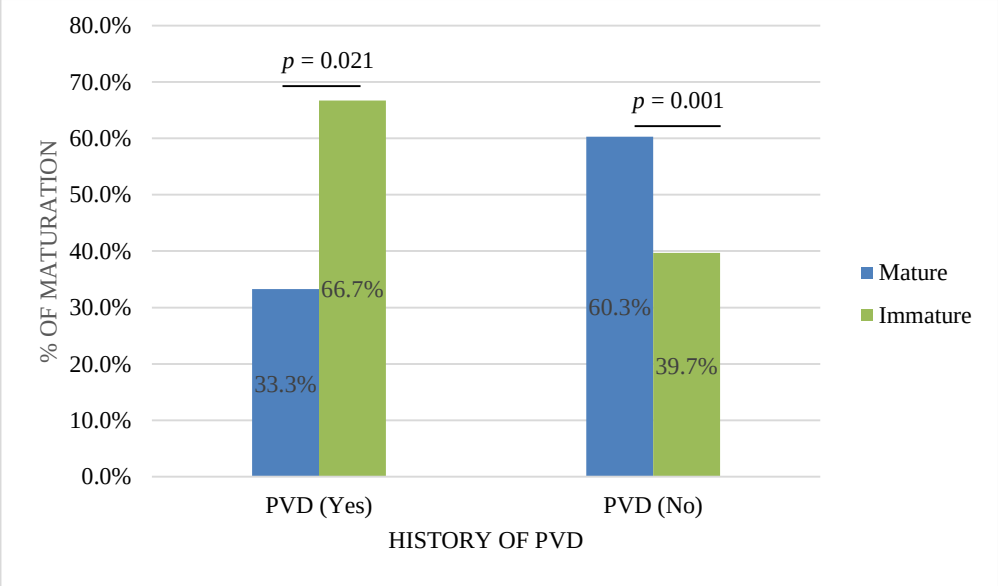


Figure 21 showing relationship between success and failure of AVF maturation in patients with presence of PVD and no history of PVD who had undergone AVF surgery. Numbers written within the bar indicated the percentage and black line over the bars indicates level of significance (Chi square) between mature and immature AVF within cohort of PVD and no history of PVD.

4.1.8 Smoking and AVF Maturation

The impact of the smoking was analysed for all participants (300) enrolled in the study. Forty one were smokers and 259 were non-smokers. Sixty one per cent (25) achieved maturation and thirty nine per cent (16) failed to mature in smokers (Table 14, Figure 23). No significant difference (p = 0.33) was found between mature and immature AVF among patients with history of smoking. The success rate of AVF was 55.2% (143) and 44.8% (116) failed to mature for haemodialysis among non-smokers (Figure 22). No significant difference (p = 0.09) was observed between mature and immature AVF among patients without history of smoking. Success of AVF maturation was not found to be associated (p = 0.49) with smoking (Table 14).

Table 14. Smoking and Maturation of Fistula

	Mature	**Immature**	**Total**	**Chi-Square**	***P* value**
Smokers	25	16	41		
Non Smokers	143	116	259	0.477	0.49
Total	168	132	300		

Table 14 shows the distribution and relationship between outcomes of AVF surgery (mature or immature) and smoking. p = 0.490 indicating that AVF surgery outcomes was independent of the presence or absence of smoking history.

Figure 22. Smoking and Maturation of AV Fistula

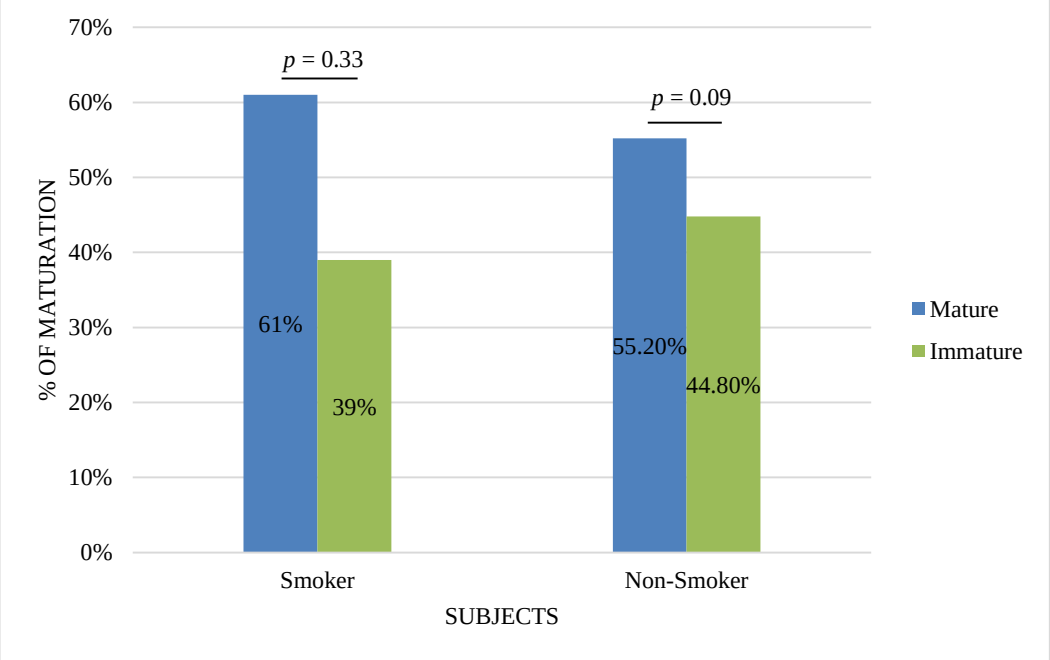


Figure 22 showing relationship between success and failure of AVF maturation among smokers and non-smokers participants who had undergone AVF surgery. Numbers written within the bar indicated the percentage and black line over the bars indicates level of significance (Chi square) between mature and immature AVF within cohort of smokers and non-smokers.

4.1.9 Dialysis and AVF Maturation

Of the 300 adults who underwent AVF formation, 112 (37.3%) went on to receive dialysis and 187 (62.7%) did not receive dialysis therapy. In the dialysis population, 60 (53.6%) AVF were successfully mature and 52 (46.4%) failed to mature (Table 15, Figure 24). Patients who had not been on dialysis before the vascular access surgery had a success rate of 57.2% (107) and failure rate of 42.8% (80) summarize in Figure 23. Significant difference (p = 0.04) was observed between mature and immature AVF among patients with no history of dialysis therapy. However, no significant difference (p = 0.45) was found between mature and immature AVF among patients receiving dialysis therapy prior to AVF creation. Success of AVF maturation was not found to be associated (p = 0.539) with dialysis therapy (Table 15).

Table 15. Dialysis and Maturation of AV Fistulae

	Mature	**Immature**	**Total**	**Chi-Square**	***P* value**
Dialysis (Yes)	60	52	112		
Dialysis (No)	107	80	187	0.378	0.539
Total	168	132	300		

Table 15 shows the distribution and relationship between outcomes of AVF surgery (mature or immature) and history haemodialysis therapy prior to AVF creation. p = 0.539 indicating that AVF surgery outcomes was independent of the presence or absence of haemodialysis therapy before AVF creation.

Figure 23. Dialysis and Maturation of Fistula

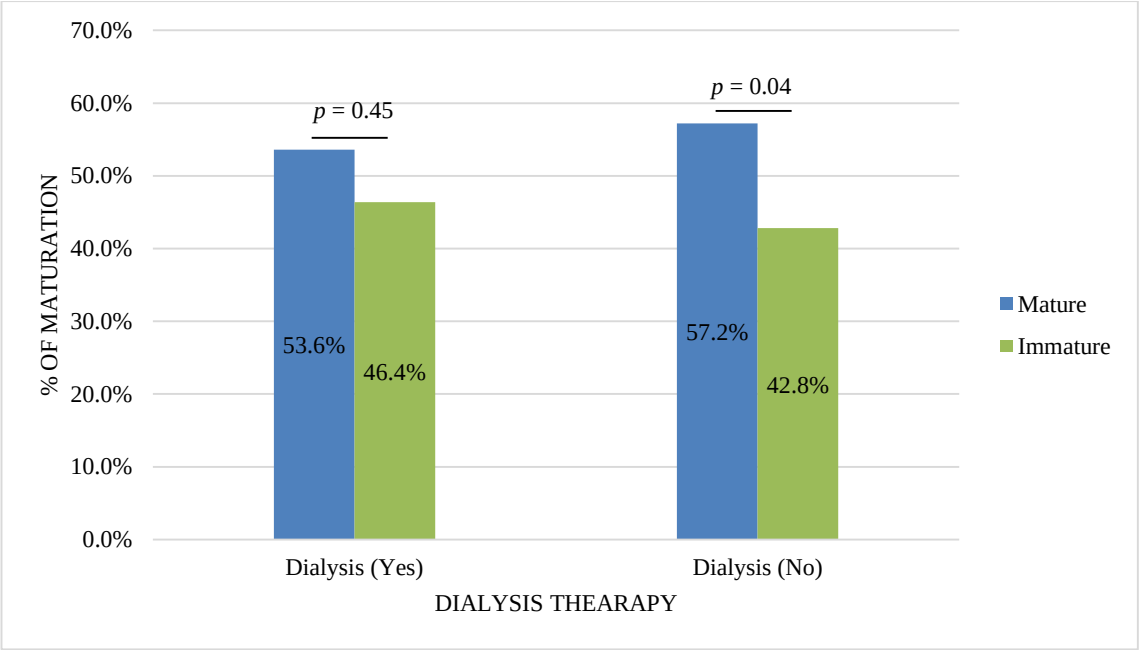


Figure 23 showing relationship between success and failure of AVF maturation in patients received dialysis therapy before AVF creation and those never have been on dialysis machine. Numbers written within the bar indicated the percentage and black line over the bars indicates level of significance (Chi square) between mature and immature AVF within cohort of patients received or not haemodialysis before creation of AVF.

4.2 Univariable Analysis of Independent Variables

A logistic regression model neither assumes linearity in the relationship between the risk factors and the response variable, nor does it require normally distributed variables (Hussain 2008). Firstly, the relationship between each individual predictor was investigated with the outcome measure (mature or immature) in a model that only included the predictor and outcome measure (univariate). The relationship between the predictor and outcome were evaluated against p-value of 0.25. If the predictor had a lower p-value, then this was considered as relevant and included in the next step. The selection strategy in this study consisted of a univariable screening step followed by stepwise multivariable selection among the univariably significant predictors. Retrospective assessment of the beginning set of 300 AVF that were constructed between 2005 and 2009 discovered a failure to mature rate of 44% (n = 132). AVF characteristic and univariable examination of clinical variables for prediction of maturation of fistula is shown in Table 16. The relationship between each individual predictor is investigated with the outcome measure. Univariable exploration discovered the nine variables to be involved with the maturation of AVF. Gender (p=0.049; OR 0.615; 95% CI 0.379, 0.998), side of arm (p=0.129; OR 1.505; 95% CI: 0.877-2.553), type of fistulae (p=0.115; OR 0.21; 95% CI: 0.423-1.208), PVD (p=0.001; OR 3.04; 95% CI: 1.585-5.829), Diabetes (p=0.102; OR 1.48; 95% CI: 0.925-2.367), SBP (p=0.101; OR 1.468; 95% CI: 0.927-2.325), INR (p=0.140; OR 0.589; 95% CI: 0.292-1.189), TG (p=0.24; OR 1.294; 95% CI: 0.804-2.084) and vein size (p<0.0001; OR 4.254; 95% CI 1.983, 9.126). A further 2 variables, Pre surgical haemodialysis (p=0.513; OR 1.17; 95% CI: 0.731-1.873) and eGFR

(*p*=0.459; OR 0.834; 95% CI: 0.516-1.349) were added to the model secondary to their strong clinical association with the maturation of AVF.

Table 16. Univariate Analysis of Independent Variables to Maturation of AVF

Clinical Characteristics	Mature AVF %	Total %	Crude OR (95% CI)	P Value
Age				0.45
> 50 yrs.	57.2	76.3		
≤ 50 yrs.	52.1	23.7	0.814(0.477-1.389)	
Gender				0.049*
Male	60	66.7		
Female	48	33.3	0.615 (0.379-0.998)	
Arm				0.129*
Left	53.4	73.7		
Right	63.3	26.3	1.505(0.887-2.553)	
Fistula				0.115*
BC	60.1	62.7		
RC	51.9	27	0.715 (0.423-1.208)	
BB	41.9	10.3	0.479 (0.222-1.036)	
Surgeons				0.788
Surgeon A	56.4	68.0		
Surgeon B	56	25.0	0.985 (0.578-1.679)	
Surgeon C	71.4	2.3	1.935 (0.367-10.206)	
Surgeon D	40	1.7	0.516(0.084-3.154)	
Surgeon E	44.4	3	0.619 (0.162-2.373)	
PVD				0.001*
Yes	33.3	16		
No	60.3	84	3.04 (1.585-5.829)	
DM				0.102*
Yes	50	38		
No	59.7	62	1.48 (0.925-2.367)	
Smoker				0.49
Yes	61	13.7		
No	55.2	86.3	0.789 (0.402-1.547)	
HTN				0.406
Yes	57.3	78		
No	51.5	22	0.793 (0.458-1.371)	
Dialysis				0.513
Yes	53.6	37.3		
No	57.4	62.7	1.17 (0.731-1.873)	
K^+				0.948
≤ 5	56.2	54.3		
> 5	55.8	45.7	1.015 (0.642-1.605)	
Na^+				0.439
≥ 135	55.1	85.3		
< 135	61.4	14.7	1.295 (0.673-2.494)	
Ca^{++}				0.525
≤ 2.5	56.7	87		
> 2.5	51.3	13	0.804(0.41-1.577)	

Table 16 continued

Clinical Characteristics	Mature AVF %	Total %	Crude OR (95% CI)	P Value
HCO3				0.743
≤ 23	57	45		
>23	55.2	55	0.926 (0.586-1.465)	
Creatinine				0.676
>400	57.5	44.7		
>120 ≤400	55.2	54.3	0.913(0.576-1.447)	
≤ 120	33.3	1	0.37 (0.033-4.182)	
Urea				0.949
>15	55.3	65.7		
>6.6-≤15	57.1	18.7	1.076 (0.591-1.960)	
≤ 6.6	57.4	15.7	1.09 (0.73-2.073)	
eGFR				0.459
≤15	57.4	64.6		
>15	52.9	35.4	0.834 (0.516-1.349)	
SBP				0.101*
≤130	51.6	53		
>130	48.4	47	1.468 (0.927-2.325)	
DBP				0.786
≤85	56.3	90.7		
>85	53.6	9.3	0.897 (0.411-1.958)	
BMI				0.563
≤30	55	73.3		
>30	58.8	26.7	1.165 (0.694-1.957)	
PT				0.413
≤ 13.4	56.9	86.6		
> 13.5	50	13.4	0.757 (0.389-1.474)	
INR				0.140*
≤ 1.2	57.6	88		
> 1.2	44.4	12	0.589 (0.292-1.189)	
TC				0.24*
≤ 5	57.9	76		
>5	50	24	1.294 (0.804-2.084)	
TG				0.289
≤ 2.1	53.7	63.3		
> 2.1	60	36.7	0.773 (0.48-1.244)	
HDL				0.874
≤ 1.1	55.6	51		
> 1.1	56.5	49	1.037 (0.658-1.637)	
Vein Size				<0.001*
≤2.5	26.3	12.6		
>2.5	60.3	87.4	4.254 (1.983-9.126)	

Independent patient factors and blood markers that underwent in univariate analysis and their association with the maturation of AVF. Data values are expressed as value (%), Odds Ratio (OR), Confidence interval (CI) and level of significance (p). *Is used for significant variables having p value <0.25, B/C-Brachiocephalic, R/C- Radiocephalic, B/B- Brachiocephalic, PVD-Peripheral Vascular Disease, DM-Diabetes Mellitus, HTN-Hypertension, K-Potassium, Na-Sodium, Ca-Calcium, HCO3-Bicarbonate, e-GFR- Estimated Glomerular Filtration Rate, SBP- Systolic Blood Pressure, DBP-Diastolic Blood Pressure, BMI- Body Mass Index, PT-Prothrombin Time, INR- International Normalization Ratio, TC- Total Cholesterol, TG- Triglyceride, HDL- High Density Lipoprotein.

4.3 Correlation

Logistic regression models often experience serious multicolinearity problems, resulting from strong correlations between independent variables. A significant correlation between variables affect the selection of predictors. It is therefore judicious to generate a correlation table, including all potential predictors. When variables are strongly correlated (correlation coefficient > 0.70), it is rational to choose which variables are going to use in building the model. However, there is no problem with variables strongly correlating with each other, i.e. the correlation between the dependent and the independent variable. A correlation coefficient was computed to assess the association among the independent variables. Overall, there was no substantial association found between independent variables summarized in Table 17.

Table 17. A Table to Show Correlation Matrix between Independent Variables

	Constant	Gender	Arm	R/C	B/B	DM	PVD	Pre HD	eGFR	SBP	INR	TC	V Size
Constant	1.0	-.072	-.173	-.272	-.099	-.276	-.423	-.385	-.177	-.246	-.008	-.105	-.666
Gender	-.072	1.0	-.046	.086	.018	.044	-.098	.070	.038	-.006	.075	-.159	-.100
Arm	-.173	-.046	1.0	-.012	.036	-.009	.004	.073	.073	.045	-.027	-.004	.047
R/C	-.272	.086	-.012	1.0	.170	-.138	-.038	-.046	-.075	.045	-.141	.033	.312
B/C	-.099	.018	.036	.170	1.0	-.039	.000	.130	-.084	.126	.062	-.069	-.057
DM	-.276	.044	-.009	-.138	-.039	1.0	-.140	.257	.070	-.012	.088	-.062	.022
PVD	-.423	-.098	.004	-.038	.000	-.140	1.0	-.006	.024	-.008	.019	.003	-.009
Pre HD	-.385	.070	.073	-.046	.130	.257	-.006	1.0	.121	.052	.006	-.061	.012
eGFR	-.177	.038	.073	-.075	-.084	.070	.024	.121	1.0	-.064	.038	.027	-.042
SBP	-.246	-.006	.045	.045	.126	-.012	-.008	.052	-.064	1.0	-.031	.021	.067
INR	-.008	.075	-.027	-.141	.062	.088	.019	.006	.038	-.031	1.0	-.042	-.144
TC	-.105	-.159	-.004	.033	-.069	-.062	.003	-.061	.027	.021	-.042	1.0	.066
V Size	-.666	-.100	.047	.312	-.057	.022	-.009	.012	-.042	.067	-.144	.066	1.0

Arm-Side of arm for AVF, R/C Radiocephalic, B/B- Brachiocephalic, PVD-Peripheral Vascular Disease, Pre HD-Haemodialysis before surgery, DM-Diabetes Mellitus, e-GFR- Estimated Glomerular Filtration Rate, SBP- Systolic Blood Pressure, INR- International normalization ratio, TC- Total Cholesterol, V Size-Vein size.

4.4 Multivariable Associations

When there are various individual predictors in the data set, model selection procedure is very helpful to develop a prognostic model that makes use of the independent predictor variables. The researcher used backward stepwise model selection procedures. In backward selection all the selected variables are firstly entered at the same time into a model. Subsequently the variables with the highest p-values are removed (i.e. those variables contributing the least). Then the model is re-run. This step is repeated until there are no variables left with a p-value greater than 0.05. Selection is based on the statistical significance of covariables in the data set under study. When the researcher entered significant variables ($p < 0.25$) in multivariable analysis, it removed non-significant variables (Table 18). An odds ratio (OR), confidence interval (CI) and level of significance was measured. An odds ratio is a measure of association between an exposure (independent variables such as gender, vein size) and an outcome (dependent variable such as maturation of AVF). The OR represents the odds that an outcome will occur given a particular exposure, compared to the odds of the outcome occurring in the absence of that exposure (Szumilas 2010). An OR of 1.00 means that the two groups were equally likely to have outcome or event (maturation). An OR higher than 1 means that the first group (no evidence of PVD group) was more likely to experience the event (maturation) than the second group (with PVD). An OR of less than 1 means that the first group (females) was less likely to experience the event (maturation) than the second group (males) (McHugh 2009).

Three variables were recognised which have an effect on fistula maturation in the multivariable model. Males were twice as likely to undergo fistula maturation,

compared to that of females (OR 0.514; 95% CI: 0.308-0.857; p = 0.011). Participants with no evidence of PVD were three times more likely to mature their fistula (OR 3.140; 95% CI: 1.596-6.177; p = 0.001). A pre-operative vein diameter greater than 2.5mm resulted in a fivefold increase in fistula maturation compared to a vein size less than 2.5mm (OR 4.532; 95% CI: 2.063-9.958; $p < 0.001$).

A predictor score developed using the regression coefficients of these independent variables is shown in Table 18. To generate a score for each predictor variables, the score is assigned by dividing Beta Coefficient to significant error. The overall probability for each patient was analysed by adding the scores of each factor. The following prognostic model was derived by using the above prediction model.

Table 18. Multivariable Predictors of AVF Maturation in the Retrospective Data

Clinical Characteristics	Adjusted OR	95% C.I.	*P* Value
Gender (Male)	0.514	0.308-0.857	0.011
PVD (No)	3.140	1.596-6.177	0.001
Vein Size (>2.5)	4.532	2.063-9.958	<0.001

The overall risk score for each patient was estimated by summing the scores of each significant independent variable. Using the prediction model, the following prognostic equation was developed:

$$\boldsymbol{Risk\ Score}(-\log \boldsymbol{odds}) = \boldsymbol{\beta_0} + \boldsymbol{\beta_1 X_1} + \boldsymbol{\beta_2 X_2} + \ldots\ldots + \boldsymbol{\beta_n X_n}$$

Where

B_0 is the intercept, β_1 till β_n are the regression coefficients and X_1 to X_n are independent variables.

$$\boldsymbol{Risk\ Score(-\log odds\ of\ failure\ of\ AVF\ maturation) = -0.182 + (-0.666 \times Gender) + (1.144 \times PVD) + (1.511 \times Vein\ Size)}$$

Where all variables are coded 0 for no or 1 for yes. The value −0.182 is called the intercept and the other numbers are the estimated regression coefficients for the predictors, which indicate their mutually adjusted relative contribution to the outcome risk.

4.4.1 Hosmer-Lemeshow Goodness of Fit Test

It is imperative to assess the performance of developed models. The hypothesis was the model does not fit and the alternative or the null hypothesis for this test was that the model fits the data. The Hosmer-Lemeshow statistic (which tests the null hypothesis is no difference between observed and predicted data) was not significant ($p > 0.79$).

4.4.2 Receiver Operating Characteristic Area

The receiver operating characteristic (ROC) area was studied as an indicator of the model performance which suggests how well a parameter can distinguish between two predictive outcomes (mature or immature). The ROC curve, which is defined as a plot of test sensitivity as the y coordinate versus its 1-specificity or false positive rate as the x coordinate, is an effective method of evaluating the performance of

prognostic model (Park *et al.* 2004). Sensitivity and specificity, which are defined as the number of true positive decisions/the number of actually positive cases and the number of true negative decisions/the number of actually negative cases, respectively, constitute the basic measures of performance of diagnostic tests (Park *et al*. 2004; Fawcett 2003) (Table 19).

Table 19. The Decision Matrix

Test Results	Positive	Negative	Total
Positive	TP	FP	TP/(TP+FP)
Negative	FN	TN	TN/(FN+TN)
Total	TP/(TP+FN)	TN/(FP+TN)	

Where TP: true positive = test positive in actually positive cases, FP: false positive = test positive in actually negative cases, FN: false negative = test negative in actually positive cases, TN: true negative = test negative in actually negative cases. Sensitivity and Specificity of a Test are Defined as TP/(TP+FN) and TN/(FP+TN) respectively. Positive predictive value and Positive predictive value are defined as TP/(TP+FP) and TN/(FN+TN) respectively.

ROC graphs are two-dimensional graphs in which true positive rate is plotted on the Y axis and false positive rate is plotted on the X axis. In this study ROC curve was created by calculating the sensitivity and specificity for consecutive cut-off points according to the predicted probabilities from the logistic regression models. The area under the ROC curve for prediction of maturation of fistula was 0.677 (95% bias-corrected CI: 0.615, 0.738), which indicates good model discrimination (Figure 24, Table 20). For binary outcomes, c is equal to the area under the ROC curve; value of c fluctuates between 0.5 and 1.0 for functional models; greater value indicates the valuable performance of prognostic model (Harrell *et al.* 1996, Miller *et al*. 1993). Tables 20 shows the best cut-off score for prediction of maturation was 0.619 (sensitivity 85.7%, specificity 40.2%, PPV 64.5% and NPV 68.8%).

Figure 24. Receiver Operating Curve Analysis for Prognostic Model Performance

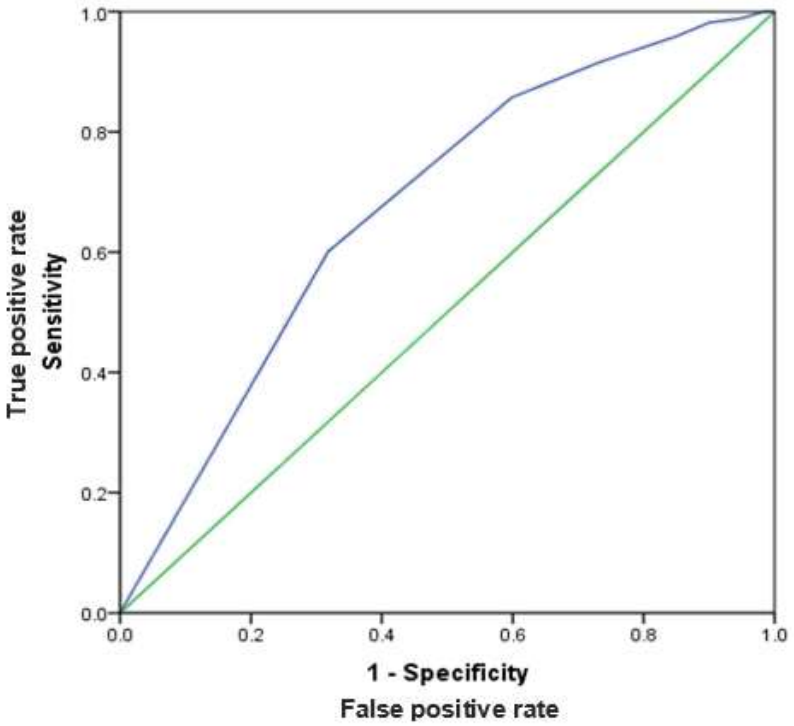


Figure 24 showing Receiver operating characteristics of AVF maturation. Area under the curve was 0.677 (95% CI: 0.615-0.738), indicating good discriminatory ability of AVF maturation.

Table 20. Specificity and Sensitivity of Model

Area under the Curve	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
0.677	85.7%	40.2%	64.5%	68.8%

Table 20 showing the area under the ROC is 0.67, which is indicating 68% ability to discriminate between patients with fistula maturation.

4.5 Validation of Prognostic Model

4.5.1 Baseline Characteristics

Clinical and demographic characteristics of patients in the development and validation sets are shown in Table 21. Patients in the development and validation set were aged 60.14±15.9 and 58±15 years respectively (p = 0.208). The significant difference between the development and validation set was evaluated against p <0.05. Baseline exploration of patients' characteristic discovered the four variables to be significantly different in both development and validation cohort. Patients in the development set compared with the patients in the validation set were more frequently male. Percentage of diabetics and peripheral vascular disease were higher in the development set. However no statistical significant difference was observed (p > 0.05). Percentage of hypertensive patients and history of prior haemodialysis therapy was statistically different in development and validation cohort. Mean of prothrombin time and total cholesterol was statistically different in development and validation set. Overall both cohort participant characteristics were similar.

Table 21. Summary of the Baseline Characteristic of Independent Variables

Characteristic	Development Set	Validation Set	*P*-Value
Gender (Male/Female)	66.7/33.3	57/43	0.08
Arm (Left/Right)	73.7/26.3	59/41	0.006*
DM (Yes/No)	38/62	28/72	0.07
HTN (Yes/No)	78/22	65/35	0.02*
PVD (Yes/No)	16/84	12/88	0.33
Smoker (Yes/No)	13.7/86.3	13/87	0.87
Dialysis prior to surgery (Yes/No)	37.3/62.7	51/49	0.02*
Type of AVF (BC/RC/BB)	63/27/10	72/20/8	0.24
BMI mean ±SD (Kg/m^2)	28±9.1	26.3±6.8	0.69
Urea, mean ±SD (mmol/L)	17.9±9	16±7.7	0.06
Creatinine, mean ±SD (µmol/L)	425±197	398±183	0.18
eGFR mean ±SD ($ml/min/1.73m^2$)	14.4±10	14.9±2.7	0.82
K, mean ±SD (mmol/L)	4.5±0.8	4.4±0.8	0.73
Na, mean ±SD (mmol/L)	140.8±31.5	138±3.9	0.04
Ca, mean ±SD (mmol/L)	2.3±0.2	2.3±0.2	0.13
HCO_3, mean ±SD (mmol/L)	24.9±5	24.8±5.1	0.85
PT, mean ±SD (second)	10.8±3.8	11.6±1.5	0.01*
INR, mean ±SD (ratio)	1.1±0.4	1±0.1	0.12
TC, mean ±SD (mmol/L)	4.3±1.3	4.5±1.4	0.05*
TG, mean ±SD (mmol/L)	2.2±1.5	2.2±1.3	0.08
HDL, mean ±SD (mmol/L)	1.2±0.5	1.2±1.1	0.07
Vein Size, mean ±SD (mm)	3.6±1	3.6±1.1	0.53

*Is used for significant difference between two cohorts p value <0.05, ±SD, Standard Deviation, DM-Diabetes Mellitus, HTN-Hypertension, PVD-Peripheral Vascular Disease, BC-Brachiocephalic, RC-Radiocephalic, BB- Brachiocephalic, BMI- Body Mass Index, e-GFR- Estimated Glomerular Filtration Rate, K-Potassium, Na-Sodium, Ca-Calcium, HCO3-Bicarbonate, PT-Prothrombin Time, INR- International Normalization Ratio, TC- Total Cholesterol, TG- Triglyceride, HDL- High Density Lipoprotein.

4.5.2 External Validation

Optimism is a well-known problem of predictive models: Their performance in new patients is often worse than expected based on performance estimated from the development data set (Harrell *et al*. 1996, Van Houwelingen and Le Cessie 1990). External validation of the prognostic model was performed by using data obtained from an independent data set of patients who received AVF at the Royal Infirmary of Edinburgh between year 2010 and 2011. The discriminative ability of the final model for the maturation of fistula was calculated by measuring the area under the ROC curve. The ROC area as the primary indicator of the model performance (Steyerberg *et al*. 2003). To assess the fit of a logistic regression model is to see what proportion of true positives it classifies as being positive (the sensitivity) and what proportion of true negatives it classifies as being negative (the specificity). Discrimination indicates how well the model discriminates between people with and without the outcome. An AUC of 0.5 indicates that the model is not discriminating very well (no different to tossing a coin); an AUC of 1.0 indicates perfect discrimination. ROC curve for external validation was developed, based on the predicted probabilities for every patient and calculating the sensitivity and specificity for consecutive cut-off points according to the predicted probabilities from the logistic regression models.

$$Predicted\ Probability = \frac{e^{(\beta_0+\beta_1X_1+\beta_2X_2+\cdots+\beta_nX_n)}}{1+e^{(\beta_0+\beta_1X_1+\beta_2X_2+\cdots+\beta_nX_n)}}$$

$$Predicted\ Probability = \frac{1}{1+e^{-(\beta_0+\beta_1X_1+\beta_2X_2+\cdots+\beta_nX_n)}}$$

Where

B_0 is the intercept, β_1 till β_n are the regression coefficients and X_1 to X_n are independent variables.

$$Predicted\ Probability = \frac{1}{1 + e^{-(-0.182+(-0.666\times Gender)+(1.144\times PVD)+(1.511\times Vein\ Size))}}$$

By using above formula predicted probability of each patient was calculated. The area under the ROC curve for the prediction of maturation of fistula was calculated using predicted probabilities and patients outcomes (mature or immature) of each patient. The area under the ROC curve for the prediction of maturation of fistula in the validation set was 0.591 (95% bias-corrected CI: 0.471-0.712), consistent with good model discrimination (Figure 25).

Figure 25. Receiver Operating Curve Analysis for Validation of Prognostic Model

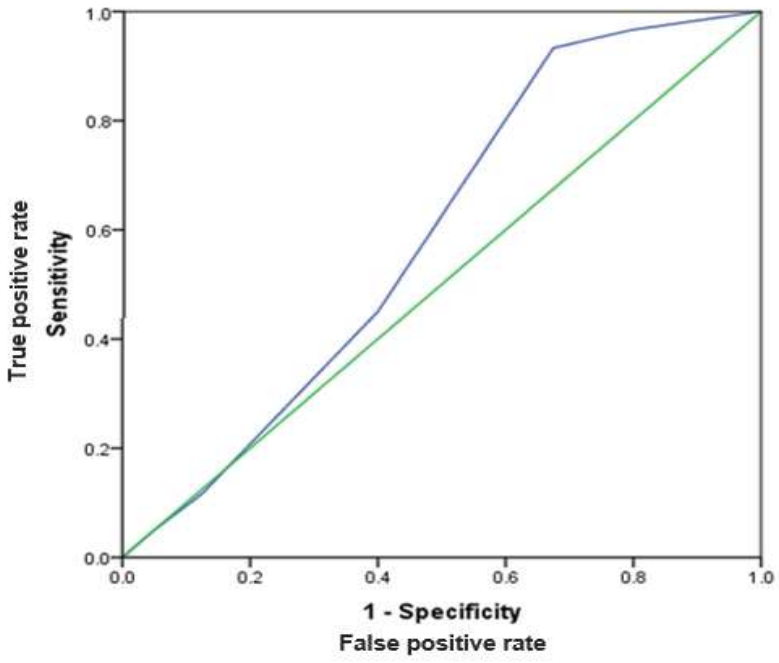


Figure 25 showing receiver operating characteristics of AVF maturation. Area under the curve was 0.591 (95% CI: 0.471-0.712), indicating good discriminatory ability of AVF maturation.

A better way of assessing the fit of a logistic regression model is compare the expected and observed numbers of positives for different subgroups of the data. If the observed and expected numbers are sufficiently close, then we can assume that we have an adequate model. In a calibration plot groups of predicted probabilities of the outcome are plotted against groups of observed probabilities. Subsequently it can assess the extent to which these groups lie along the perfect calibration line, which forms a 45 degree angle with the horizontal axis (Steyerberg 2009; Harrell 2001). The calibration ability of the validation model for the maturation of the fistula is shown in plot (Figure 26). Predicted and observed values lie along the calibration line, which forms a 45 degree angle with the horizontal axis.

Figure 26. Calibration Plot of the Prediction Model

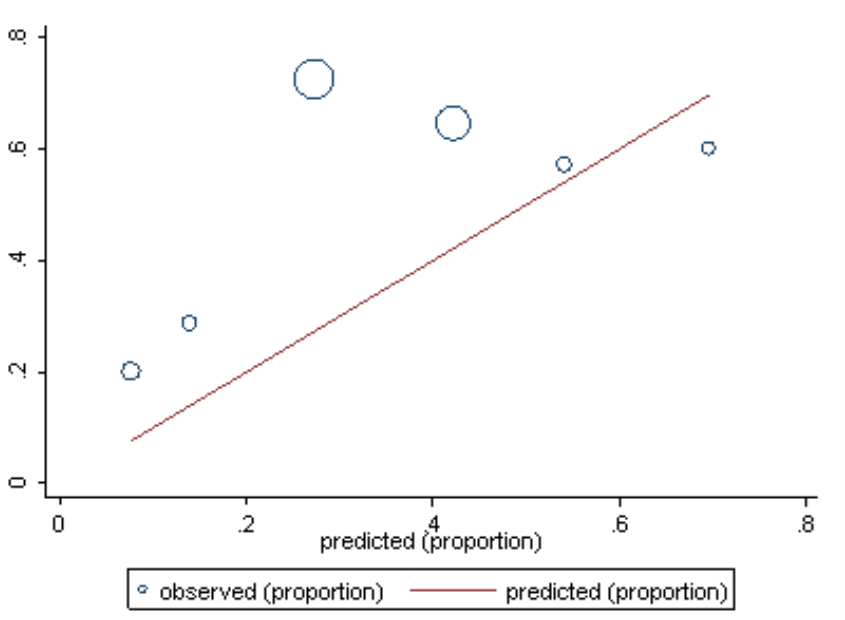


Figure 26 showing calibration plot in which groups of predicted probabilities of the outcome (mature or immature) are plotted against groups of observed probabilities. Figure shows groups lie along the calibration line, which forms a 45 degree angle with the horizontal axis.

CHAPTER 5

DISCUSSION

5.1 Success Rate of AVF Maturation

This study set out with the aim of assessing the importance of independent markers in the prediction of maturation of AVF. The results of this study identify three clinical factors, each of which was independently associated with maturation of AVF: male gender, PVD, and vein diameter. AVF efficiently developed in 168 patients, accounting for 56% of the total number of patients. Similar results have been obtained by Feldman *et al.* (1993), with 44.5% out of a total of 348 patients exhibiting unsuccessful AVF development. This high percentage is not surprising, taking into consideration the various problems of development that have always characterised the fistula, as well as the problems related to the process of dialysis. If a fistula fails to mature at four to eight weeks, then it is not likely to be available for cannulation later on (Kian and Vassalotti 2005; Robbin *et al*. 2002), especially without intervention.

5.2 Age and AVF Maturation

In this study, age of patient was not found to be an independent marker of AVF maturation in univariable and multivariable analysis. In a similar manner, the study results achieved by Renaud *et al*. (2012) indicated that neither the primary nor the secondary accessibility of the radiocephalic and brachiocephalic AVF, nor their applicability, was influenced by age. Demographic and clinical factors affecting fistula maturation were retrospectively compared among 280 patients with incident ESRD at a single centre. Study results suggested that primary fistula strategy in elderly ESRD patients is feasible and does not result in inferior outcomes. Age should therefore not be a determinant for primary fistula creation. Similarly Weale *et*

al. (2008) identified the outcomes of all patients undergoing a first surgical access procedure for a radiocephalic and brachiocephalic AVF. From a total of 658 patients, 361 had a radiocephalic, and 297 had a brachiocephalic AVF. The study results concluded that age do not affect usability, primary or secondary patency of either radiocephalic or brachiocephalic AVF. Bessias *et al.* (2008) argued that, despite the fact that it is essential to choose patients accordingly, any patients, irrespective of age, can undergo this surgical procedure, provided that they are considered capable of withstanding it.

In this study 76.3%, participants were aged more than 50 years and 23.7% were aged below 50 years. Nowadays, ESRD is usually encountered mostly in old patients who also suffer from other related conditions, including hypertension, diabetes, and obesity. In particular, the combination of age and diabetes impairs fistula outcome with significantly higher failure rates up to 42% (Tordoir *et al*. 2007). The association between increasing age and greater risk for failure to mature is related with the normal aging process and are damaged by concurrent disease; this finding is supported by other studies (Feldman *et al.* 2003; Huber *et al.* 2002). The results obtained by other researchers (Swindlehurst *et al.* 2011; Peterson *et al.* 2008; Lok *et al*. 2006; Miller *et al.* 1999b), corroborate the findings of previous research regarding the direct connection between advanced age and underdeveloped fistula. Lok *et al*. (2006) observed that older patients generally had a greater risk of AVF maturation failure (hazard ratio, 1.7) than those with higher age, but that secondary patency was equivalent between age groups for all types of autogenous access. A recent meta-analysis of thirteen relevant studies (all cohort observational studies, 11 retrospective) were included. The meta-analysis results revealed a statistically

significantly higher rate of radial-cephalic AVF failure in elderly patients compared with non-elderly adults at 12 (odds ratio [OR], 1.525; $p = 0.001$) and 24 months (OR, 1.357, $p = 0.019$). The primary radial-cephalic AVF rate was also in favour of the non-elderly adults (OR, 1.79; $p = 0.012$). Secondary analysis revealed a pooled effect in favour of the brachiocephalic AVF that was statistically significant ($p = .004$) compared with distal fistulas in elderly patients and has recommended that this finding should be considered when planning access surgery (Lazarides *et al.* 2007). However, the definitions of "elderly" in the included studies ranged from 50 to 70 years, and the review was specific to wrist AVFs.

5.3 Gender and AVF Maturation

The present study results indicate a gender difference in the maturation of AVF, mature rates of 60% for men and of 48% for women. Miller *et al.* (1999b) found that the AVF creation is more successful in men than in women. Similar results were obtained by El Ters *et al*. (2012), Iyem (2011) and Gibbons (2006). This study also revealed that the efficiency of fistula development in men is double, in comparison to women (OR being 0.514 and the 95% CI: 0.308 to 0.857). A number of other studies (Wolford *et al*. 2005; Ernandez *et al*. 2005; Patel *et al*. 2003; Feldman *et al*. 2003; Prischl *et al*. 1995; Solomonson *et al*. 1994) which examined agents related to AVF adequacy or patency supported this result; the most rational explanation for this difference is the smaller size of vessels in women. Moreover, women within the study population often had diabetes mellitus or hypertension or were classified as "early postmenopausal", all of which are conditions that may produce a form of atherosclerosis that accelerates more rapidly than that in men (Schild 2010). In this

study gender emerged as a significant marker for the prediction of maturation of AVF in both univariate (OR – 0.615; $p = 0.049$) and multivariate (OR - 0.514; $p = 0.011$) analysis. Some other studies also found female gender to be associated with immature fistula (Peterson *et al.* 2008; Lok *et al*. 2006; Huber *et al*. 2002; Robbin *et al.* 2002; Thomsen *et al.* 1983; Kinnaert *et al.* 1977). It is commonly believed that the vascular anatomical differences between the two different genders influence to decreased creation of AVF in women. However, Caplin *et al.* (2003) employed a group of 192 patients to carry out detailed mapping of upper arm vessels using duplex Doppler ultrasonography. The diameter of the blood vessels was measured at 29 locations (17 on the vein and 12 on the artery). Comparison of the measurements revealed that there was no considerable distinction in the vein diameter between men and women at any location. Other studies have demonstrated that the sex differentiation is also minimal. Palmes *et al*. (2011) did not find any gender differences on AVF patency in elderly patients. In their study, that involved the creation of 132 AVFs on 114 subjects, Baser *et al.* (2006) did not observe any gender differentiations with regard to initial or delayed maturation failure of the AVFs or in their patency. Similarly, Erkut *et al.* (2006) did not find any sex distinctions in the evaluation of the efficiency of AVFs in a sample group composed of 310 men and 102 women. Ekicei *et al.* (2008) found no considerable gender distinctions in the success rate of AVFs either.

5.4 Right/Left Fistula and AVF Maturation

AVF was generally created at the distal end compare to proximal location and of the less used arm compare to dominant arm to preserve dominant arm to allow daily

living activities. Arterial inflow is a key component that is necessary for AVF maturation. A native vein fistula that has poor inflow from the artery fails to dilate and develop into a usable access for haemodialysis. In this study success rate of maturation was 53.4% in left side AVF and 63.3% was in right sided AVF. The researcher found side of arm significant in the univariate analysis but did not show significance in the multivariable analysis. This finding is supported by a retrospective analysis of a prospective computerized vascular access database performed by Shingarev *et al*. (2012) to compare primary failure and cumulative survival of upper extremity AVFs and AVGs. Among those patients received an AVF (233 patients), neither the primary failure rate nor cumulative access survival differed significantly between AVFs placed in the right and left upper extremities. It might seem obvious, the ideal time to assess which arm has the best vessel for an AVF is before the first AV access is placed and when patient's hopes and confidence are high. After one or more failed procedures in the non dominant arm, it is harder for the patients to accept switching to the dominant side. These technical and emotional difficulties can be avoided by the rule that AVF should be placed in the arm with the best vessels regardless or side of arm. A single centre, randomised study was conducted by Koksoy *et al*. (2009) to compare outcome, patency, and complication rates in these two autogenous upper arm AV accesses (B/B AVF or B/C AVF). A total of 100 patients (50 B/C and 50 B/B AVF) were recruited and univariate analysis showed that risk factors associated with poorer patency rates to be use of dominant arm for fistula creation. The smaller sample size may have obscured this association in this investigation.

5.6 Type of Fistula and AVF Maturation

In the current study, 62.7% of AVF were brachiocephalic, 27% were radiocephalic, and 10.3% were brachiobasilic. The results indicate 60% brachiocephalic, 52% radiocephalic and 42% brachiobasilic AVF were successfully mature and adequate for cannulation. However, due to the fact that predictive and pathophysiological factors are directly linked, the positioning of the AVF in the forearm or arm had no effect on the study prediction model as a suitable inflow and outflow are necessary regardless of the position of the fistula. The results of the present study are coherent with other studies (Koksoy *et al*. 2009; Saran *et al*. 2004; Robbin *et al*. 2002) whereas Miller *et al.* (1999b) discovered that fistulas in the upper arm are more likely to develop successfully and Monroy-Cuadros *et al.* (2010) results showed that forearm fistula are independently associated with loss of primary patency. Lazarides *et al.* (2007) carried out meta-analysis of the results of the dialysis access in old individuals and found an increased risk of AVF failure in the forearm and significant maturation of brachiocephalic fistulas. In the case of patients who have no suitable vessels in the lower arm, it may be possible to create brachiobasilic fistula in the arm. The constriction or blockage of the cephalic vein in the antecubital area, where it often undergoes the process of cannulation for phlebotomy, can hinder the creation of a fistula. On the other hand, the basilic vein can withstand the creation of a fistula as it is of considerable diameter and it is not so close to the surface as the cephalic vein and thus it is not punctured during the phlebotomy. Nevertheless, as noted by Oliver *et al.* (2001), the fact that it is not a superficial vein means that the basilic vein cannot undergo cannulation of a brachiobasilic fistula in its original location. One solution would be to section and gouge out the basilic vein in the superficial tissue

layer of the forearm, where it could be reached with a dialysis needle. However, at present, there is no general agreement as to which method of AVF is most suitable. In this study success rate of forearm AVF was lower than upper arm and that is consistent with previous studies (Peterson *et al*. 2008; Lok *et al*. 2006). Arteriosclerosis is usually more manifest distally, a more proximal fistula location at the proximal forearm, the elbow and upper arm region may be advantageous in elderly CKD patients suffering from diabetes and peripheral arterial disease (Palmes *et al*. 2011; Allon *et al*. 2000). However, the incidence of thrombotic and infectious complications is low and long-term outcome is good (Fitzgerald *et al.* 2004). There is one important negative aspect of positioning a fistula at the elbow; namely, a risk of high blood flow, which can cause distal hypo-perfusion as well as elevated output heart failure, especially in individuals with ischaemic cardiac disease (van Hoek *et al*. 2006; Fitzgerald *et al.* 2004).

5.7 Surgeon and AVF Maturation

The construction of fistulas was undertaken by surgeons with significant experience. The main objective of these surgical procedures was to expand the development success rate of fistulas, regardless of the pre-surgery assessment and the actual operation. The surgeons carried out the procedures themselves (rather than training residents), relying on their vast experience. These differences in surgeon were found to have no influence in the outcome of surgery. However, the findings of the current study do not support the previous research that indicates that surgical selection is a major predictor of AVF success rate and outcome (Kats and Wasse 2008). The study conducted by Huijbregts *et al.* (2007) focused on determining alterable and

unalterable agents, which play a part in the initial functionality of the AVF in eleven medical centres in the Netherlands. It was demonstrated that the likelihood of initial maturation failure has a close correlation to the location of the AVF, highlighting the importance of the decisions made by the surgeons, as well as their capabilities.

An emphasis on haemodialysis access procedures and number of AVFs created during surgical training influences the type of access created and AVF survival (Saran *et al*. 2008). In addition, surgical centre volume (Greater than 30 access procedures per year), surgeon volume, and surgical subspecialty have all been shown to increase the creation of AVFs over arteriovenous grafts (Choi *et al*. 2008; O'Hareet *et al*. 2003; Lazarides *et al*. 2002). Overall, early nephrology referral and timely referral to a dedicated surgeon, in co-operation with a multidisciplinary team, offer the progressive kidney disease patient the best chance of using an AVF at the initiation of dialysis.

5.8 PVD and AVF Maturation

The presence of peripheral vascular disease has been associated with an increased risk of AVF failure because an insufficient artery or vein may be unable to increase blood flow sufficiently and undergo adequate maturation. Modern high-frequency ultrasound machines capable of high-resolution imaging can determine the intima media thickness of small arteries such as the radial artery at the wrist. Ku *et al.* (2006) reported that intima media thickness measurements during preoperative duplex ultrasound imaging correlated significantly to histologic measures and, more importantly, to AVF thrombosis and to inadequacy of an AVF to maintain dialysis at 1 year. Similarly, ankle-brachial pressure index, a reliable marker for peripheral

vascular disease, had a significant association with access failure after adjusting for other variables (Chen *et al.* 2009). The result of this study showed that AVF maturation rate was 59.7% in a group with no history of PVD and 33.3 in patients with PVD. In current study, PVD emerged as one of the predictive markers in the maturation of fistula in both univariate and multivariate analysis. The chances of patients without peripheral vascular disease to attain full development of the fistula increased threefold. Similar results have been obtained by Lok *et al*. (2006) and Woods *et al.* (1997) also discovered a connection between PVD and AVF success rate. According to one study, the attributable risk of AVF failure from PVD was 24% higher and may carry a relative risk three times normal (Woods *et al*. 1997). Obialo *et al.* (2003) observed a PVD associated relative risk of 1.9. There is a high prevalence of PVD in diabetic patients (83% in this study). By extension, vascular access failure rates are predictably high among diabetic patients (Dixon *et al.* 2002; Miller *et al.* 1999b). Chan *et al*. (2008) conducted a retrospective cohort analysis using 1486 patients' data. It was revealed that patients who suffer from PVD are more likely to experience failure of AVF maturation (OR 2.78, 95% CI 1.01–7.63, $p = 0.047$). A large multicentre study data comprising of 6400 patients from 145 US dialysis units and 101 units in five Europe countries (France, Germany, Italy, Spain, and the United Kingdom) was found AVF to be strongly related ($P < 0.01$) to the absence of peripheral vascular disease (Pisoni *et al.* 2002). In contrast a retrospective study (Peterson *et al*. 2008) of 205 patients did not find a significant association between fistula maturation and peripheral vascular disease. The smaller sample size may have obscured this association in this investigation.

5.9 Diabetes and AVF Maturation

European patients have a less propensity to have diabetes than Americans but still have substantial comorbidity (Mendelssohn *et al.* 2005). The current study comprise of 38% diabetic in which rate of AVF maturation was 50%. Diabetes as an independent predictor was significant in univariate analysis but after multivariable analysis, the researcher did not find it as a predictor of maturation. This finding is in agreement with Ekicei *et al.* (2008) and Wolowczyk *et al.* (2000) findings, which showed diabetes has no effect on AVF maturation rates. A number of studies (Allon *et al.* 2000; Hirth *et al.* 1996), have debated whether diabetes increases the likelihood of fistula failure or occurs as a result of other factors and conditions, including sex (women are more likely to develop diabetes), advanced age, obesity or PVD. Although this finding corroborates the findings of Feldman's and other studies (Monroy-Cuadros *et al*. 2010; Huijbregts *et al*. 2008; Patel *et al*. 2003; Obialo *et al*. 2003). In contrast, these results differ from some published studies (Ernandez *et al*. 2005, Miller *et al*. 1999b) which demonstrated diabetic state did not significantly change AVF maturation rate. However, other studies have omitted PVD or employed a more broad characterization (Lauvao *et al*. 2009; Wolford *et al*. 2005). PVD often accompanies diabetes, becoming integrated in the symptoms of diabetes; thus, it is overlooked as a disease in its own right. Cheng Wu *et al.* (2010) and Robbin *et al.* (2002) discussed the negative effect of diabetes on the structure of the veins, which makes them unsuitable for the construction of fistulas.

Sedlacek *et al*. (2001) reported that despite increased arterial calcification, vessel diameters and arterial peak systolic volume were not significantly different between

diabetic and non-diabetic patients in their population. Subsequent AVF formation in their diabetic patients was effective, and outcomes were similar regardless of the presence of diabetes. Konner *et al*. (2002) reported increased use of proximal fistulas in diabetic patients but with primary access survival similar to that of non-diabetic patients. Secondary survival at 24 months was reduced compared with non-diabetic subjects, however, and steal syndrome was more common in the diabetic group. Functional maturity rates for AVFs in diabetic patients have been suggested to be increased by the use of routine vessel mapping (Konner *et al*. 2002). As such, the effects of diabetes on overall AVF outcomes may be minimized by careful preoperative vessel imaging and AVF site selection.

5.10 Smoking and AVF Maturation

Ozdemir *et al.* (2005) drew attention to the threat posed by smoking to the development of vascular blockages in all patients, irrespective of whether or not they suffer from ESRD. Few studies have investigated the history of smoking in the context of the rate of incidence of vascular disease, but no conclusive results were obtained (Churchill *et al*. 1992; Reilly *et al.* 1982). Previous peripheral vascular damage in former and active smokers may lead to acute access thrombosis, which may partially explain the inconsistency in results. Surprisingly, the prevalence of smoking in this study participant was very low (13.7%). This result may be explained by the fact that the poor data transcription (Data transcription is the process of converting voice-recorded reports, procedures and notes as dictated by physicians or other healthcare professionals, into text format in order to create files representing the treatment history of patients). The results of this study did not show the

maturation difference of AVF in smoking and non-smoking group (61% and 55.2% respectively). This study did not detect any evidence of smoking as an independent marker for the prediction of maturation of AVF. However, recent study (Kaygin *et al.* 2012) findings showed strong association between AVF outcomes and smoking habits. According to Ozdemir *et al.* (2005), the possibility of occurrence of AVF thrombosis is increased by smoking and a high number of eosinophils. Wetzig *et al*. (1985) found that the failure rate of AVF maturation (early and delayed) among patients with haemodialysis who smoked regularly was considerably higher. The discrepancies in the results can be attributed, in part, to acute access thrombosis caused by previous peripheral vascular disruptions in erstwhile and current smokers. A number of endothelial cells functions are affected by the substances derived from cigarette smoking such as nicotine, carbon monoxide and tar. In the long run, the ability of endothelial cells of anticoagulation can be affected, as can their ability to prevent the formation of blockages and reduced their fibrinolytic activity. What is more, smoking can alter vaso-dilatation, which depends on the endothelium by disrupting the processing and release of nitric oxide. As explained by Newby (1999), a diminished quantity of nitric oxide can determine a growth in the compression, multiplication, and movement of vascular smooth muscle cells. Thus, smoking can lead to constriction as well as blockage of blood vessels, affecting the AVF.

5.11 Hypertension and AVF Maturation

In this study, 78% of all patients had a history of arterial hypertension, which was distinguished as independent risk factors (systolic blood pressure) associated with a decreased AVF maturation rate in univariate analysis. However, hypertension did not

find to be a significant predictor of maturation in multivariable analysis. The findings of the current study are consistent with those of Monroy-Cuadros *et al.* (2010) who did not show a significant association between hypertension and AVF maturation. Results of another retrospective study including 298 vascular access procedures concluded that hypertension, tobacco use, and prior dialysis catheter placement had no effect on fistula maturation by univariate or multivariate analysis (Lauvao *et al*. 2009).

Although, these results differ from Kaygin *et al*. (2012) who observed a negative association between hypertension and fistula maturation. Similarly results of a retrospective study of 105 patients found arterial hypertension as an independent risk factor that was significantly associated with AVF failure (OR: 3.4; 95% CI: 1.1–9.9) (Palmes *et al*. 2011). AVF maturation depends on the availability of a suitable vein and likewise on the ability of the artery to dilate, the dispensability of the arterial wall being an additional factor (Kheda *et al*. 2010). Since, during the primary fistula creation, more vessel calcifications were detected in diabetics and hypertensive patients, a more proximal fistula location has proven successful for fistula maturation (Chin *et al*. 2004; Konner 2000).

5.12 Dialysis and AVF Maturation

In this study, the success rate was 57.4% who have not been on dialysis before and in contrast 53.6% success rate in the patients on dialysis. The researcher included variable in multivariable analysis, but did not find to have any impact on fistula maturation in this study. This finding is in agreement with Palmes *et al.* (2011) findings, which suggested no any impact of dialysis treatment before surgery on the

patency rate and fistula maturation. However, the findings of the current study do not support the recent research, which found earlier utilization of central venous catheters as a strong independent risk factor for lack of AVF maturation (El Ters *et al*. 2012; Erkut *et al.* 2006).

The assessment of the accomplishments and drawbacks of AVF construction over a two year period at one institution, prior to the commencement of dialysis, has been carried out by Weber *et al.* (2009). It was revealed that AVF construction prior to dialysis had a success rate of 72%. According to Arora *et al.* (1999), 40% of the patients who have been referred to a kidney specialist in the early stages of renal disease exhibited a functional vascular access upon commencement of dialysis, in contrast to 4% of the patients who have been referred to a specialist in the late stages of the disease. Astor *et al.* (2001) noted that in patients referred early the initial vascular access is a fistula rather than a graft, as in the patients with late referral. In the case of the delay, the accessibility and development of the fistula can be disrupted by the use of a provisional CVC to start the dialysis. Catheter complications can lead to a premature fistula cannulation with consecutive AVF failure due to haematoma formation, fibrosis, and damage to the great vein (Ravani *et al*. 2004; Avorn *et al*. 2002; Roubicek *et al*. 2000).

5.13 Electrolytes, Urea, Creatinine and eGFR and AVF Maturation

Aronson *et al.* (1996) have drawn attention to the fact that disruptions to the metabolism determined by diabetes can lead to pro-thrombotic condition, endothelial dysfunction, deregulation of the growth factor, and augmentation of the extracellular matrix deposition. Whilst undergoing dialysis, the risk of hyperkalaemia is

considerably high among patients with progressive renal disease. This is caused by external intake of potassium or by abrupt disruption of the potassium sources from the interior to the exterior of the cells. In the present study success rate of maturation was 57.8% and 56.2% in patients having an abnormal value of potassium (45.7%) and with normal value of potassium (54.3%) respectively. The study did not find the potassium as a predictor of maturation as it was not significant in univariate and multivariate analysis.

In chronic kidney disease, the acidosis is normally mild and the concentration of serum bicarbonate does not usually decrease below 15-18 mmol/L until the start of the ESRD (Palevsky 2004). In the present study, 45% of the participants had less than 23 mmol/L of bicarbonate, whereas the other 55% exceeded this amount. The development rate did not display any substantial discrepancies, with 57% in the former group and 55.2% in the latter.

Chronic kidney disease is generally accompanied by mild hypocalcaemia, which is a disruption of calcium homeostasis that occurs often. This condition does not create particular problems in the pre-surgery interval (Slatopolsky and Hruska 2001). In the present study, the level of serum calcium of 87% of patients was below 2.5 mmol/L whilst the level of serum calcium of 13% of patients exceeded 2.5 mmol/L. Different haemostatic disruptions are considered to be the cause of bleeding diathesis and pro-thrombotic condition in uraemia. However, we did not find urea, Creatinine and eGFR as predictive markers for the maturation of fistula. Bhan *et al*. (2007) found a rapid loss of eGFR in the year preceding dialysis was a significant negative predictor for a fistula however, eGFR at dialysis start was not found to be a significant marker.

5.14 BMI and AVF Maturation

As noted by Fouque *et al.* (2007), the body mass index (BMI) is the standard method used in studies of epidemiology to calculate body size, as well as in evaluations of dietary status and supervision in ESRD. Surprisingly, no considerable discrepancies with regard to the development rate between patients with a BMI lower and greater than 30 kg/m^2 were recorded in the present study, the development rate being 55% and 58.8%, respectively. In the present study, BMI did not emerge as an independent predictive marker in both univariate and multivariable analysis. Nevertheless, Miller *et al.* (1999b) discovered that patients with a BMI lower than 27 kg/m^2 had a decreased possibility of the AVF developing into a functional access. According to Stehman-Breen *et al.* (2000), every standard deviation exceeding the average BMI of a patient was accompanied by a 30% decrease in the possibility of constructing AVF, in contrast to AVG. This result was corroborated by Polkinghorne *et al.* (2003), who noted the likelihood of patients with a BMI greater than 30 kg/m^2 to have an AVG increased with 79%. Obesity is considered to be one of the agents that can have a negative impact on the efficacious creation of AVF (Allon e*t al.* 2000). A recent study was conducted by Gagliardi *et al*. (2012) to evaluate the role of body mass index on arteriovenous fistula dysfunction in 84 patients. The study results did not find BMI as an independent predictor of thrombosis and stenosis of AVF.

There can be no doubt about the connection between obesity and diabetes, which increases the risk of developing advanced arterial occlusive disease especially in the lower arm, thus having a negative effect on the development of AVF. A number of researchers (Colli and Sirtori 2010; Eichinger *et al.* 2008; Yusuf *et al.* 2005) have

observed that obesity increases the chances of developing venous and arterial thrombosis, which could have a negative influence on AVF access. Colli and Sirtori (2010) explained that, despite the fact that the manner in which obesity determines vascular thrombosis is, as yet, unknown, it has been observed that the adipokines and pro-inflammatory cytokines generated by the adipose tissue determine a growth in the number of pro-coagulant proteins, fibrinogen and factor VII. However, this biochemical connection between obesity and vascular thrombosis has not helped to identify exactly how obesity leads to the development of initial AVF thrombosis, particularly as the arteriovenous accesses have considerable blood flow. Initial AVF thrombosis in two obese female patients with a BMI of 34 kg/m^2 and 39 kg/m^2, respectively, was found by Plumb *et al.* (2007) to develop as a result of anatomic factors, namely, the obstruction of the axillary-subclavian veins during arm flexion. The study conducted by Kats *et al.* (2007) focused on determining the AVF development success rate in a group of 183 patients, of which 54 were obese and 129 had a normal weight. The results revealed that the likelihood of initial AVF breakdown between the two groups was relatively the same, with 46% in the obese and 41% in the normal weight patients.

5.15 Clotting Factor (PT, INR) and AVF Maturation

Early AVF failure occurs in up to 60% of newly created AVFs, and results from thrombosis or marked in-flow stenosis, leading to non-maturation (Dember *et al*. 2008; Dember and Dixon 2007). The typical lesion of vascular access thrombosis is neointimal vascular smooth muscle cell proliferation in the anastomotic draining vein. Platelet activation from endothelial injury may play an important role in

stimulating platelet aggregators such as platelet-derived growth factor and thromboxane A2, in addition to directly stimulating vascular intimal proliferation (Roy-Chaudhury *et al*. 2006). In patients suffering from uraemia, the development of thrombosis could be confusing, as uraemia is generally accompanied by bleeding diathesis. It is well-known that patients with ESRD experience abnormal bleeding. On the contrary, advanced intravascular coagulation could be a sign of thrombosis. In order for the fistula to develop, it is highly important to keep access unblocked, as it is difficult to reconstruct if vascular thrombosis develops during the initial couple of weeks subsequent to the construction of the fistula. On this basis, it has been conjectured that deterrence of fistula breakdown increases its chances of developing fully.

In the present study, multivariable analysis did not corroborate the hypothesis that fistula access is favourably influenced by high pro-thrombin time and international normalised ratio (INR), despite the considerable values displayed by the earlier in univariate analysis. Even if coagulation and vascular obstruction are avoided, fistula development could still be hampered by constriction of the draining vein. As noted by Kaufman (2000), initial fistula blockage can be prevented by applying anti-platelet agents, thus contributing to increase the AVF development success rate. In a study conducted by the Dialysis Access Consortium, 877 patients with newly constructed fistulae were randomly selected to have clopidogrel and placebo administered for a month and a half (Dember *et al.* 2008). The administration of clopidogrel determined a considerable decrease in the development of initial fistula thrombosis of 12.2% in contrast to 19.5%; however, a percentage of 61.8% and

59.5% of fistulae in both groups were inadequate for dialysis within half a year of their construction.

Ghorbani *et al.* (2009) conducted a double-blind, randomized trial to determine the effects of clopidogrel on the incidence of primary AVF failure among newly created AVFs in ninety three patients. Study results showed a significant risk reduction in the primary AVF failure in active treatment group compared to placebo group. These results were supported by a Cochrane report (Da Silva *et al.* 2003). This meta-analysis confirmed the beneficial effect of antiplatelet treatment as an adjuvant to increase the patency of AVFs in the short term. However, there have been multiple studies showing variable results of antiplatelet agents on vascular access failure. Yevzlin *et al.* (2006) showed a negative association between antiplatelet therapy and access patency. Previous double-blind randomized study has conducted to determine the association of antiplatelet drug ticlopidine with AVF maturation; however, none has found a beneficial effect on the maturation of AVF. In the study over 1 month, two of six fistulas in the ticlopidine group and five of nine in the placebo group failed. A further one placebo and two ticlopidine patients still had functioning fistulas at the time of withdrawal for technical reasons from the trial. Ticlopidine appears, therefore, to enhance the efficacy of fistulas, at least in the short term (Fiskerstrand *et al.* 1985).

In contrast, the association between vascular access patency and the use of specific drugs was studied in a large sample of US haemodialysis patients enrolled in the Dialysis Outcomes and Practice Patterns Study, an international, prospective, observational study. Study results did not find an association of aspirin and warfarin

therapy with AVF maturation (Saran *et al*. 2002). The differences between the effects of high PT and INR on fistula maturation and patency may be an indication that thrombosis is a manifestation of AVF failure, and not the cause of it. Further research is required to find more efficient methods of increasing the fistula success rate, particularly with regard to the influence of the vascular function and anatomy on fistula development.

5.16 Lipid Profile (TC, TG, HDL) and AVF Maturation

In the current study, well established proatherogenic factors; hypercholesterolemia, triglycerides, and high-density lipoproteins, did not influence the risk of AVF maturation. A similar result was observed in a retrospective study including 298 vascular access procedures concluded that hyperlipidaemia had no effect on fistula maturation by univariate or multivariate analysis (Lauvao *et al*. 2009). The results of this study show that 76% participants having their cholesterol level equal or below 5 mmol/L. Total cholesterol was found significant in univariate analysis but no significant influence was found on the maturation in multivariable analysis. However, results of a recent case controlled study conducted in the Italy (Gagliardi *et al*. 2011) suggested that the total plasma cholesterol is an important risk factor of AVF failure in haemodialysis patients. However, the patient numbers (91) were relatively small in the study. The success of the maturation was 53.7% in patients having a triglyceride value below 2.1 mmol/L and 60% was in those having above 2.1 mmol/L. Overall this study did not demonstrate any significant association between lipid profile and AVF maturation. Between 20 and 80% of patients that had undergone renal replacement therapy exhibited hyperlipidaemia with a growth in the

levels of cholesterol and triglyceride (Tse *et al*. 2004; Castelao *et al*. 1992). The results of a retrospective study (Kirkpantur *et al*. 2008) suggested that not TC, but lipid sub fractions (LDL-C and HDL-C) were associated with AVF thrombosis. Atherosclerosis has the potential to promote thrombotic events in the venous system or the two conditions (atherosclerosis and venous thrombosis) may share common risk factors like dyslipidaemia (Prandoni 2007; Prandoni *et al.* 2003). Previous studies of serum from ESRD patients have documented decreased HDL-C and LDL-C, increased small dense LDL particles, and elevated TGs level with a normal TC level compared with the general population (Quaschning *et al.* 2001; Deighan *et al*. 2000. Hulthe *et al.* 2000) indicated that all components of this type of dyslipidaemia are independently atherogenic. Therefore, focusing on TC alone may underestimate the complex atherogenic dyslipidaemia associated with uraemia and the presence of a lipid profile consistent with uraemic dyslipidaemia in the context of normal plasma TC highlights the need to look beyond the basic assessment of plasma concentrations of TC when assessing the AVF thrombosis risk to be presented by dyslipidaemia in maintenance haemodialysis patients (Kirkpantur *et al*. 2008).

5.17 Vein Diameter and AVF Maturation

In this series of 300 patients undergoing AVF access creation success of maturation was 60.3% in a group having vein diameter greater than 2.5 mm and 26.3 % in equal or smaller than 2.5 mm vein size. The result of this study found vein diameter is strongly significant independent predictive marker (p<0.001) in the maturation of fistula both in univariate and multivariate analysis. A pre-operative vein diameter greater than 2.5 mm resulted in a fivefold increase in fistula maturation compared to

a vein size less than 2.5 mm (OR 4.532; 95% CI 2.063 to 9.958). The results of the current study are consistent with Zadeh *et al*. (2012) and Lauvao *et al.* (2009) findings, which showed, vein diameter associated with successful maturation of fistula. Wong *et al.* (2011) also discovered that initial fistula failure can be brought about if the diameter of the radial artery and cephalic vein is below 1.6 mm. Kinnaert *et al.* (1977) proposed that the reduced dimensions of blood vessels in women makes them more predisposed to developing AVF failure. The results of a current prospective, observational study (Jemcov 2013) showed that female gender was associated with prolonged maturation of AVF, having a significantly smaller radial artery compared to men. . If the diameter of the cephalic veins exceeds 2 mm, there is a 76% success rate of functional dialysis access, whereas if the diameter is less than 2 mm, there is only a 16% success rate (Mendes *et al.* 2002). The pre-surgery ultrasound scan generates valuable data regarding vein thickness, compressibility, anatomic diversity and veins depth below the skin. The cut-off value identified by Brimble *et al.* (2002) was 2.6 mm; however, only women exhibited a substantial discrepancy between AVF success and failure with regard to vein diameter. In contrast, Wong *et al.* (1996) did not observe any discrepancies between AVF success and failure in the mean vein diameter at the wrist, but indicated AVF failure in all cases where the vein diameter was below 1.6 mm. Korten *et al.* (2007), on the other hand, did not observe any connection between vessel diameter and fistula development.

It is important for the draining vein to have a particular size in order to ensure needle access as well as appropriate blood flow. Furthermore, fistulae, which have increased chances of developing, and those which have not have to be differentiated. Enhanced

vascular access is believed to be favoured by the use of pre-surgery vascular mapping (KDOQI 2006). This can offer the surgeon important data about vessel diameter, and the occurrence of vessel stenosis or thrombosis (Allon and Lok 2010). Assessment of haemodialysis access can be made with the help of ultrasonography, the fact that it is easily accessible, non-invasive, and relatively cheap, making it an efficient technique. Furthermore, this technique eliminates the hazards, which accompany the use of iodinated contrast material and ionizing radiation. One of the objectives of the present study was to verify whether the diameter of the outflow vein could be used as an indicator of fistula development.

What is more, fistula development also depends on an adequate supply of intra-access blood and pressure, which, in turn, rely on efficient heart output/systemic blood pressure as well as a supply vessel of high quality, capable of shifting the high pressure to a secondary, flexible, and dilatable outflow vein. According to Lyem (2011), the risk of early fistula thrombosis could be reduced by mechanical distension of the blood vessels prior to commencing anastomosis and the use of agents that cause dilatation of vessels.

Preoperative Vein Mapping

Robbin *et al.* (2002) suggested that ultrasonography may help to identify early fistula suitability and is even capable of generating predicted markers, if the anatomic as well as the functional parameters are employed. The kidney specialist and the vascular surgeon can refer to the predicted markers to better organise the procedure. Patel *et al.* (2003) revealed that patients who underwent physical examinations prior to surgery had an 80% maturation rate. It is possible that vessels, which can be

discerned and palpated during a general examination, differ from the vessels, which can be identified only through radiologic imaging. A number of researchers (Parmley *et al.* 2002; Huber *et al.* 2002; Robbin *et al.* 2000; Silva *et al.* 1998) have drawn attention to the fact that the use of pre-surgery imaging protocols, such as routine venous duplex ultrasonography scanning, in association with selective venography and arteriography may involve considerable risks, as it was observed that they were employed in cases where there was a growth in AVF preponderance.

5.18 Validation of Prognostic Model for Maturation of AVF

The efficiency of a predictive model has to be tested on a new group of subjects. In the present case, the performance of the predictive model with regard to the external verification of fistulae that had been constructed in the same hospital was good. The purpose of a predictive model is to assess potential risks and to manage treatment accordingly, to ensure the success of the AVF construction procedure. This practice can help to structure the process, ensure efficient management of resource distribution, and limit expenses. The ultimate objective is to expand the number of successfully created, permanent accesses and limit CVC reliance and its implicit risks.

The long-term objective of this research effort was to identify factors predicting fistula maturation. The purpose of this study was to develop and validate a prognostic model in the prediction of AVF. We hypothesized that blood and patient factors could be used to stratify risk of self-report of maturation of AVF. In brief, using the development dataset of 300 subjects, we identified three variables

associated with maturation of fistula: gender, PVD and vein size and these variables were validated by using validation dataset of 100 subjects.

As highlighted by Wong *et al.* (1996), most of the times, the kidney specialist or the vascular surgeons are unable to remedy certain risk factors, such as vessel diameter or properties, and intravascular blood flow. In the present study, it was the first time that the patients had fistulae constructed so the predictive model regarding earlier fistula failures could not be applied. Feldman *et al.* (2003) revealed that fistulae constructed for patients who had had earlier fistulae had an increased likelihood of successful development. However, our prognostic model performed well in the external validation of fistulae that involved patients who had not experienced earlier AVF creation or failure. Despite the fact that the external validation was illustrative of patients who had received first time AVF with an acceptable sample size of 100 participants, the verification did not take into account the medical recommendations with regard to the risk factors associated with AVF maturation failure.

The performance of the developed model in this study was assessed by discrimination and calibration of the model. The area under the ROC curve for a prognostic model is classically between 0.6 and 0.85 (Royston *et al*. 2009). In our study ROC curves was primarily designed for prognostic models, rather for diagnostic models. ROC curve was 0.68 in the development model and 0.59 in the validation stage, meaning that the model had reasonable capacity to correctly distinguish between mature and immature fistulae. For clinical practice, providing insight beyond the *c* statistic has been a motivation for some recent measures, especially in the context of extension of a prediction model with additional predictive

information from a biomarker or other sources (Cook 2007; Pencina *et al.* 2008; Pepe *et al*. 2008)

Accuracy of the model was assessed by examining calibration (Grzegorczyk-Martin *et al.* 2012). To assess the validity of the predictive model developed using the development dataset, we applied the model to an independent or a validation dataset composed of 100 subjects. There was excellent agreement between the predicted and observed percentage in predicting maturation of AVF**.** We further note that a substantial size will be required for a validation sample to quantify validity in a reliable way, i.e. with enough power to substantial decrease in discriminative ability (Steyerberg *et al.* 2004).

CHAPTER 6

CONCLUSIONS

This chapter will provide a summary of the study, relate the findings with their implications, discuss the limitations of this study, and suggest possible directions for future studies.

6.1 Conclusion of Study

Successful vascular access provision is the foundation on which successful haemodialysis is built. This thesis has provided a detailed evaluation of the risks to health conferred by some of the key elements of haemodialysis AVF provision and maintenance. In order to identify which fistulae have greater potential to develop, a pre-surgery prediction rule was formulated and thoroughly verified. It was facile and could be readily employed in predictive risk classification systems. Three factors were recognized as being important indicators of AVF development, namely, gender, peripheral vascular disease, and vein diameter. Due to time restrictions, assessments were carried out pre operatively and post operatively without a further follow up assessment, which could provide information on the longer-term consequences. However, additional assessment of the clinical benefits of such a risk classification system in relation to AVF development, based on a larger sample, is necessary. It is of considerable importance that many of the issues described in this thesis continue to be explored, solutions developed, and outcomes improved in this especially large population of vulnerable patients. The safe and effective provision of haemodialysis vascular access therefore remains an area in which considerable improvements in the health of renal patients may be made in the future.

6.2 Clinical Implication of Research

Determining the type of vascular access has prime significance for maximizing a successful maturation of fistula and avoiding surgical revision. Unfortunately, despite being a common form of surgery performed today, there are no consistent criteria that can be applied before creation of arteriovenous fistula at present. The surgeon has to rely on his clinical judgement and other investigatory parameters including a pre-operative duplex scan, which has a major role in determining the success of maturation of fistula. However, it is not an entirely reliable tool and should be used only as one of the factors rather than the only factor to determine the maturation of fistula. This study makes this complex decision making easier and adds to the lists of the markers, which can play a role in the successful maturation of fistula.

This study has an impact not just on the patients but also on the staff involved in the creation of AVF including revision procedure, and other type of vascular access after failure of AVF maturation. The failure of maturation has an impact not just on the patient but also the health system. The three factors, which the study has shown to be of significance, namely gender, PVD and vein diameter that are routinely done on patients in a clinical setting.

Despite the fact that AVF failure is more frequent in women than in men, the many benefits of the AVF procedure are an indication that it should be used more often-in women as well. If undertaken correctly, there is no reason why AVFs in women should not reach a similar success rate observed with men. The risk factors

previously identified can be relied upon to structure a more efficient AVF screening protocol.

The challenge that both medical specialists and patients will soon be confronted with is related to the high cost of the staged method of AVF development, which can require several operations. As stated by Manns *et al.* (2005), most of the people suffering from chronic kidney disease are admitted to hospital for vascular surgery, which, together with its associated problems, poses a considerable financial strain on health care institutions.

6.3 Limitations of Research

The present study has a number of limitations. The formulation of the prediction rule relied on 400 fistulae, constructed in the same medical centre in Scotland. It is possible that the recorded incidence of diabetes, peripheral vascular disease, and smoking is not illustrative of all the dialysis patients in Scotland.

Second, the fistulae were constructed by surgeons who had a great deal of experience and were familiar with the procedure. The objective of the surgeons was to carry out the procedure in spite of the differences between pre-surgery examination and the actual intervention. The surgeons conducted the operations themselves; they did not delegate the task to interns. However, there were few staff changes during the five years when the fistulae were constructed. As argued by Pisoni *et al.* (2002), it is important to take into consideration non-measurable elements, such as surgical techniques, and principles of care, apart from ample case-mix adaptations highlighted by other studies.

Third, the surgical factor, intra-operative heparin, was not taken into account in this study (Feldman *et al.* 2003). The study aimed to identify the cases in which such an intervention would have been suitable, given the fact that it was proven to influence fistula development, and also considering available resources and expenses.

Fourth, the connection between artery diameter and blood inflow rate was emphasised by a number of studies (Zadeh *et al*. 2012; Monroy-Cuadros *et al.* 2010; Parmar *et al*. 2007; Huijbregts *et al.* 2009). However, we did not included artery diameter and arterial blood flow in our study due to the unavailability of retrospective data.

Another limitation was the duplex measurements of the vein diameter, that were carried out a single time represents an additional drawback of this study. Measurements of vessel diameter carried out during different times of day can show discrepancies. Day-to-day variations in venous diameter might have been due to differences in venous dilatation due to alterations in vascular tone (Planken *et al*. 2006). Other factors such as temperature, physical activity, mental state, may also affect vessel breadth as it determines the dilatation of the vessels.

Another limitation of this study was the considerable discrepancies in the measurements of vessel diameter in the same individual and between sonographers also represent a drawback. Despite the effort put into monitoring every potential source of inconsistency, inter-observer discrepancies in the patient sample were largely disregarded.

6.4 Future Research

Further research studies are needed to determine how to predict, prevent, or treat failure of AVF maturation. In order to offer clinically meaningful solutions, have need of larger, multicentre trials. The quantity of patients needed for such a study will depend on the selection of primary outcome selected and the estimated event rates.

Hyperparathyroidism observed in about half of all patients associated with significantly higher patency rates especially after forearm AVF and represented an independent protective factor related with fistula patency in the multivariate analysis (Palmes *et al.* 2011). Other published studies describe hyperparathyroidism as an independent risk factor for vascular access thrombosis, probably induced by micro calcification of the vessel wall (Diehm *et al*. 2010; Grandaliano *et al*. 2003; Rostand and Drueke 1999). Further investigations are necessary to clarify a potential relationship between hyperparathyroidism and vascular access patency. The beneficial effect of hyperparathyroidism on fistula patency and maturation warrants more extensive investigations.

Recent studies have shown an important role of matrix metalloproteinase in the process of AVF maturation (Berceli, *et al*. 2006; Chan *et al*. 2007). A promising biomarker identified in human vein tissue, matrix metalloproteinase-2, may serve to predict AVF maturation (Lee et al. 2010). We did not look at matrix metalloproteinase as predicative marker. However, further studies are needed compare the relative importance of other matrix metalloproteinase isoforms in the process of AVF maturation.

Additional follow-up time is prerequisite to get hold of further understanding into long-term AVF patency.

This study can have several follow-up studies. One of them could be the role of endothelial dysfunction markers in relation to the maturation of AVF. Some of the endothelial dysfunction markers including Endothelin-1, von Willibrand factor, vascular endothelial growth factor (VEGF) and homocysteine, have been shown to be useful predictors to determine maturation of AVF in patients who underwent AVF surgery.

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Appendix I - Participant Information Sheet

Queen Margaret University

EDINBURGH

Participant Information Sheet

Role of blood indicators and factors in predicting fistula maturation in patients with kidney failure

School of Health Sciences

Queen Margaret University

Edinburgh

We would like to invite you to take part in a research study examining the role of blood indicators such as blood clotting indicator, blood cholesterol, blood sugar, kidney functions and ultrasound imaging in predicting success of arteriovenous fistulae in patients with kidney failure.

Before you decide if you would like to participate, you need to understand why the research is being done and what it would involve for you. ***Please take time to read the information carefully***. Talk to others about the study if you wish.

Feel free to ask any question if there is anything that is not clear or if you would like more information. Contact details are at the end of the document.

What treatment is available for kidney failure?

The treatment for kidney failure is dialysis. Dialysis is a way of removing the waste products from the blood stream when the kidneys cannot cope. It is like having an artificial kidney.

Dialysis is a method that requires access to the blood stream. In other words it is a connection between the blood stream and the artificial kidney (dialysis machine).

What is fistula and how it works?

A direct connection between an artery and a vein is created at a surgical operation that is known as *arteriovenous fistulae*. After arteriovenous fistulae formation the veins expand and the veins walls become much thicker over a period of 6 weeks that is known as *maturation of fistulae*. This is because arterial blood at a higher pressure is now flowing through the vein. When dialysis is required needles are inserted into the vessels and connected to a dialysis machine.

What is the purpose of this study?

The purpose of the study is to explore the relationship between the blood indicators and success of arteriovenous fistulae maturation. These indicators include blood clotting indicator, blood cholesterol, blood sugar, kidney functions and ultrasound imaging.

Am I suitable?

You can participate in this study if you have kidney diseases with history of diabetes or hypertension, planned creation of upper arm arteriovenous fistula for dialysis. Unfortunately you cannot participate if you are pregnant, breastfeeding, or plan to be

pregnant during the course of the study, presence of on-going bleeding, on anticoagulant therapy or current history of chest pain.

Do I have to participate?

You participation in this research is entirely voluntary. The information pack given to you contains this information sheet and a consent form. Should you agree to participate, you will be required to sign the consent form before participation. You are free to withdraw at any time, without giving a reason.

What will happen if I take part?

Once your consent is obtained you will be assessed on the day of Duplex scan prior to fistula creation. It will last for approximately 30 minutes. Your visit plan will be as follows:

All assessments will be conducted at the same time of day (+/-1 hour). Both the assessors are familiar with the testing equipment and procedure, one being a qualified nurse and the other vascular surgeon.

At the time of your assessments, the following will happen:

- At each visit you will have the chance to ask questions and raise any issues before, during and after each assessment.
- Before surgery general physical examination and your weight and height will be measured
- Before surgery your blood sample (1) will be taken and then the blood vessels diameter and blood flow will be measured using ultrasound device (2)

- After the surgery, physical examination and assessment of fistulae with ultrasound device will be carried out.

For the assessment, you will have to remove your, jacket and outer clothing so that your weight and height are accurately recorded and your clothing does not interfere with the measurements.

1) *For the blood analysis about 10ml (2 tea spoons) blood will be obtained by inserting a needle into a vein in the arm. Blood sample will be taken by NHS staff as a regular procedure for pre operative tests. From these blood tests we will calculate your kidney function status, blood clotting profile, blood sugar level and blood cholesterol level.*

2) *The ultrasound is a non-invasive method of obtaining pictures of the arteries and veins of the arm similar to that used for pregnant women to observe an unborn baby. The technique uses sound waves to construct a scan (picture). It is therefore not harmful in any way. We will look specifically around your upper arm. The test will require you to be lying down and will involve the placement of a small device on the skin of your arm. A sticky gel will be used to improve the quality of scan. The gel wipes and washes off easily and will not stain your skin or clothes.*

Will there be any disadvantages of taking part?

Taking part in this study will not put you at risk of any bodily or mental harm. Your health status will not be altered in anyway by taking part.

We will need access to your whole arm for vessels diameter and blood flow for the ultrasound assessment. For your comfort and ease of testing, it is recommended that you wear a sleeveless top for the assessment. Assessments will be carried out with respect for your privacy and your comfort will be ensured before and during the entire period of assessment.

What are the benefits of taking part in the study?

You may learn about your body composition.

What if there is a problem?

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. If you have a concern about any aspect of this study, you could ask to speak to me and I will do my best to answer your questions (Queen Margaret University telephone: 01314740000). Alternatively, you could also contact the independent advisor (contact details given), if you should wish to complain formally.

What if I do not want to continue my participation?

You are free to withdraw from the study at any given point without having to give a reason for doing so.

Will my taking part in the study be kept confidential?

All information about you collected during the course of the study will be kept securely and will be accessible only to the research team members.

All information, which is collected, about you during the course of the research will be kept strictly confidential.

All data will be anonymised as much as possible, and you will not be identifiable from any of the data collected from you. Your name will be replaced with a participant number and it will not be possible for you to be identified in any reporting of the data gathered.

What will happen to the results of the study?

If you are interested in the overall results of the study, these will be emailed to you as once the study complete.

The results may be published in a journal, presented at a conference, or used as a part of a PhD thesis. Your anonymity will be preserved.

Who has reviewed the study?

This study has been reviewed and given favourable ethical opinion by the Queen Margaret University Research Ethics Committee

For further information contact details:

Name of researcher: Muhammad A Siddiqui

Address: Postgraduate Research Student
School of Health Sciences
Queen Margaret University
Queen Margaret University Drive,
Musselburgh,
EH216UU

Email / Telephone: msiddiqui@qmu.ac.uk / 0131 474 0000

Contact detail for independent advice

Name: Dr. Paddy Gibson

Address: Consultant Kidney Physician
Royal Infirmary of Edinburgh
51 Little France Crescent
Old Dalkeith Road
Edinburgh
EH16 4SA

Email: paddy.gibson@luht.scot.nhs.uk

If you have read and understood this information sheet, any questions you had have been answered, and you would like to be a participant in the study, please now see the consent form.

Appendix II- NHS EthicalApproval

Lothian NHS Board

Deaconess House
148 Pleasance
Edinburgh
EH8 9RS
Telephone 0131 536 9000
Fax 0131 536 9009
www.nhslothian.scot.nhs.uk

NHS Lothian

South East Scotland Research Ethics Committee 03

Deaconess House
148 Pleasance
Edinburgh
EH8 9RS

Telephone: 0131 536 9022
Facsimile:

22 July 2009

Dr Muhammad Siddiqui
Queen Margaret University
School of Health Sciences
Queen Margaret University drive
EH21 6UU

Dear Dr Siddiqui,

Study Title: **Role of haematological markers and factors in predicting fistula maturation in patients with renal failure: An Exploratory Study**
REC reference number: **09/S1103/29**
Protocol number: **1.3**

The Research Ethics Committee reviewed the above application at the meeting held on 08 July 2009.

Ethical opinion
The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Ethical review of research sites
The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

The favourable opinion applies to the following research site(s):

Research Site	Principal Investigator / Local Collaborator
Royal Infirmary of Edinburgh	Dr Muhammad Siddiqui

Conditions of the favourable opinion
The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

For NHS research sites only, management permission for research ("R&D approval") should

be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk. Where the only involvement of the NHS organisation is as a Participant Identification Centre, management permission for research is not required but the R&D office should be notified of the study. Guidance should be sought from the R&D office where necessary.

It is responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents
The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Compensation Arrangements		31 July 2008
Statistician Comments		22 May 2009
Application		21 May 2009
Participant Consent Form	1.2	21 May 2009
Protocol	1.3	21 May 2009
Participant Contact Details	1.2	21 May 2009
Investigator CV	CI Siddiqui	21 May 2009
Investigator CV	Carline	
Investigator CV	Raza	
Investigator CV	Santos	
Investigator CV	Walker	
Recruitment procedure clarification		22 July 2009
Participant Information Sheet	1.4	05 July 2009
Covering Letter		26 June 2009
Response to Request for Further Information		22 July 2009

Statement of compliance
The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review
Now that you have completed the application process please visit the National Research Ethics Service website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

09/S1103/29	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project

Yours sincerely

Dr Christine West
Chair

Email: joyce.clearie@nhslothian.scot.nhs.uk

Copy to: *Professor Marie Donaghy*
QMU
QMU Drive
RH21 6UU

R&D QMRI

South East Scotland Research Ethics Committee 03

LIST OF SITES WITH A FAVOURABLE ETHICAL OPINION

For all studies requiring site-specific assessment, this form is issued by the main REC to the Chief Investigator and sponsor with the favourable opinion letter and following subsequent notifications from site assessors. For issue 2 onwards, all sites with a favourable opinion are listed, adding the new sites approved.

REC reference number:	09/S1103/29	**Issue number:**	2	**Date of issue:**	22 July 2009
Chief Investigator:	Dr Muhammad Siddiqui				
Full title of study:	Role of haematological markers and factors in predicting fistula maturation in patients with renal failure:An Exploratory Study				

This study was given a favourable ethical opinion by South East Scotland Research Ethics Committee 03 on 08 July 2009. The favourable opinion is extended to each of the sites listed below. The research may commence at each NHS site when management approval from the relevant NHS care organisation has been confirmed.

Principal Investigator	*Post*	*Research site*	*Site assessor*	*Date of favourable opinion for this site*	*Notes [1]*
Dr Muhammad Siddiqui	PhD Student	Royal Infirmary of Edinburgh	South East Scotland Research Ethics Committee 03	22/07/2009	

Approved by the Chair on behalf of the REC:

..... (Signature of Chair/Co-ordinator)

(delete as applicable)

J CLERKE ..... (Name)

(1) *The notes column may be used by the main REC to record the early closure or withdrawal of a site (where notified by the Chief Investigator or sponsor), the suspension of termination of the favourable opinion for an individual site, or any other relevant development. The date should be recorded.*

University Hospitals Division
Queen's Medical Research Institute
47 Little France Crescent, Edinburgh, EH16 4TJ

NHS Lothian

CPP/JB/approval/2e,3,3b

13 August 2009

Dr Muhammad Siddiqui
PhD Student, School of Health Sciences
Queens Margaret University
Queens Margaret University Drive
Musselburgh
EH21 6UU

RESEARCH & DEVELOPMENT
Room E1.12
Tel: 0131 242 3330
Fax: 0131 242 3343
Email:
R&DOffice@luht.scot.nhs.uk

Director:
Professor David E Newby

Dear Dr Siddiqui

MREC No:	**N/A**
CRF No:	**N/A**
LREC No:	**09/S1103/29**
R&D ID No:	**2009/R/VS/01**
Title of Research:	*Role of haematological markers and factors in predicting fistula maturation in patients with renal failure: An Exploratory Study*
Protocol No/Acronym:	**Version 1.3 no date**

The above project has undergone an assessment of risk to NHS Lothian and review of resource and financial implications. I am satisfied that all the necessary arrangements have been set in place and that all Departments contributing to the project have been informed.

I note that this is a single centre study sponsored by **Queen Margaret University.**

Use of Tissue or Samples

- The study involves the use of patient tissue or samples. You must be familiar with NHS Lothian's Tissue Policy and abide by its conditions and also with all regulations in place at the time. Approval is subject to the prevailing legal requirements.
- Approval for the use of tissue is restricted to the protocol associated with this application. You are reminded that explicit consent must be obtained for storage and use in possible future research projects. Collaborators who are not named in the original protocol require to be notified to local Research Ethics Committee.
- I note that additional samples will be taken for the study and that this will be done with the patient's explicit consent.

On behalf of the Chief Executive and Medical Director, I am happy to grant management approval from NHS Lothian to allow the project to commence, subject to the approval of the appropriate Research Ethics Committee(s) having also been obtained. Please note that this letter also provides Site Specific approval for **NHS Lothian.** You should note that any substantial amendments must be notified to the relevant Research Ethics Committee and to R&D Management with approval being granted from both before the amendments are made.

This letter of approval is your assurance that NHS Lothian is satisfied with this project. For approved research, NHS Lothian will provide cover for negligence for NHS and Honorary clinical staff for research associated with their clinical duties. It is not empowered to provide non-negligent indemnity cover for patients.

As Chief Investigator or local Principal Investigator, you should be fully committed to your responsibilities within the Research Governance Framework for Health and Community Care, an extract of which is attached to this letter.

Yours sincerely

CPhillips

Dr Christine P Phillips
Deputy R&D Director

enc **Research Governance Certificate** ☑ **(to be signed and returned)**
Tissue Policy (if applicable) ☐

"Improving health through excellence and innovation in clinical research"

Appendix III- Consent Form

Queen Margaret University
EDINBURGH

CONSENT FORM

Title of Project:

"**The Role of haematological markers and factors in predicting fistula maturation in patients with renal failure: An Exploratory Study"**

Please initial box

1. I confirm that I have read and understood the information sheet and this consent form. I have had an opportunity to ask questions about my participation. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that sections of any of my medical notes may be looked at by responsible Individuals (Research Team) or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐

4. I agree to take part in the above study. ☐

_____	_____	_____
Name of Patient	Date	Signature
_____	_____	
Researcher	Date	Signature

Contact details of the researcher:
Name of researcher: Dr Muhammad A Siddiqui
Address: PhD Student, Podiatry, School of Health Sciences
Queen Margaret University
Edinburgh, EH21 6UU
Email / Telephone: MSiddiqui@qmu.ac.uk / 0131 474 0000

1 for patient; 1 for researcher; 1 to be kept with hospital notes

Appendix IV - Insurance Letter

MARSH

MARSH MERCER KROLL
GUY CARPENTER OLIVER WYMAN

Marsh Ltd
Glasgow
Postal Address:
PO Box 3262
Norwich, NR7 7BH
0141 304 4386 Fax 0141 221 5409
Tommy.Masterson@marsh.com
www.marsh.co.uk

31st July 2008

Subject:
To Whom It May Concern

Dear Sirs

EVIDENCE OF INSURANCE – QUEEN MARGARET UNIVERSITY

We are writing to confirm that we act as Insurance Brokers to the above client and that we have arranged liability insurance on their behalf as detailed below:

EMPLOYERS LIABILITY

INSURER	Royal & Sun Alliance
POLICY NUMBER	RTT153481
PERIOD OF INSURANCE	1st August 2008 – 31st July 2009 both days inclusive
LIMIT OF LIABILITY	£10,000,000

PUBLIC/PRODUCTS LIABILITY

INSURER	Royal & Sun Alliance
POLICY NUMBER	RTT153481
PERIOD OF INSURANCE	1st August 2008 – 31st July 2009 both days inclusive
LIMIT OF LIABILITY	£10,000,000 any one occurrence unlimited in the period of insurance for Public Liability and in the aggregate in the period of insurance for Products Liability

EXCESS EMPLOYERS LIABILITY

INSURER	ACE Insurance
POLICY NUMBER	UKCASO01497108
PERIOD OF INSURANCE	1st August 2008 – 31st July 2009 both days inclusive
LIMIT OF LIABILITY	£15,000,000 in excess of £10,000,000 (insured by Royal & Sun Alliance) any one occurrence

MARSH

MARSH MERCER KROLL
GUY CARPENTER OLIVER WYMAN

EXCESS PUBLIC/PRODUCTS LIABILITY

INSURER	ACE Insurance
POLICY NUMBER	UKCASO01497108
PERIOD OF INSURANCE	1st August 2008 – 31st July 2009 both days inclusive
LIMIT OF LIABILITY	£10,000,000 in excess of £10,000,000 (insured by Royal & SunAlliance) any one occurrence unlimited in the Period of Insurance for Public Liability and in the aggregate in the Period of Insurance for Product Liability

PROFESSIONAL INDEMNITY

INSURER	Royal & Sun Alliance
POLICY NUMBER	RKK415215
PERIOD OF INSURANCE	1st August 2008 – 31st July 2009 both days inclusive
LIMIT OF LIABILITY	£3,000,000 each and every claim and in the aggregate

Standard policy terms, conditions and exceptions apply to all policies.

This letter is issued as a matter of information only and confers no rights upon the recipient of this letter other than those provided by the policy. This letter does not amend, extend or alter the coverage afforded by the policy or policies as described herein.

Notwithstanding any requirement, term or condition of any contract or other document with respect to which this letter may be issued or pertain, the insurance afforded by the policy (policies) described herein is subject to all terms, conditions or exclusions of such policy (policies). Limits shown may have been reduced by paid claims.

If you should require any further information on the above please do not hesitate to contact us.

Yours sincerely

Tommy Masterson
Client Adviser